

Diabetic Kidney Disease (DKD):

“ THE CURRENT PARADIGM ”



Saddam Hassan

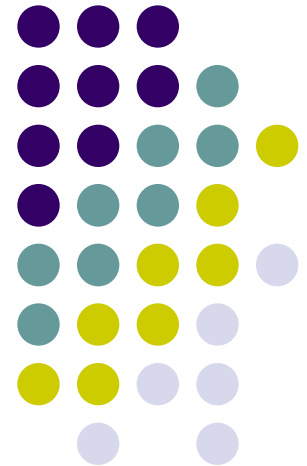
MD

Lecturer of Nephrology

Nephrology UNIT

Benha University

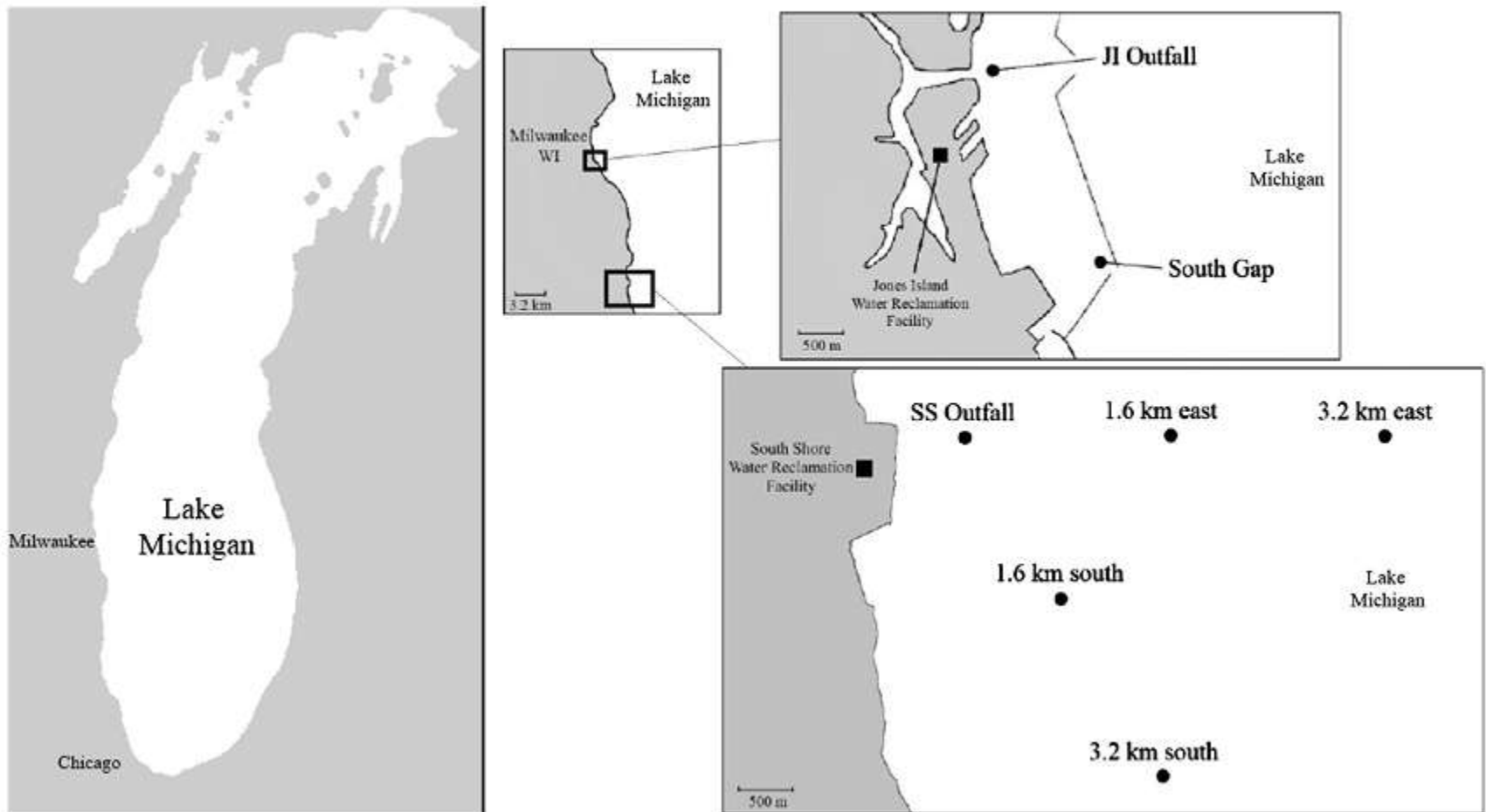
February 2015

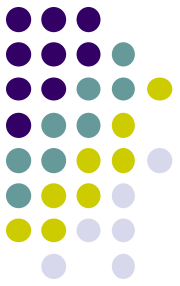


Metformin Lakes



B.D. Blair et al. / Chemosphere 93 (2013) 2116–2123





 **“ From Bench to Bedside “**
Glomerular or Tubuloglomerular?

 **“ Conventional Paradigm “**
Does Benefit justify Risk ?

 **“ Opportunities or Challenges “**
Multi-Pathway Signal Blockade ?



“ From Bench to Bedside “

Glomerular or Tubuloglomerular?



“ Conventional Paradigm “

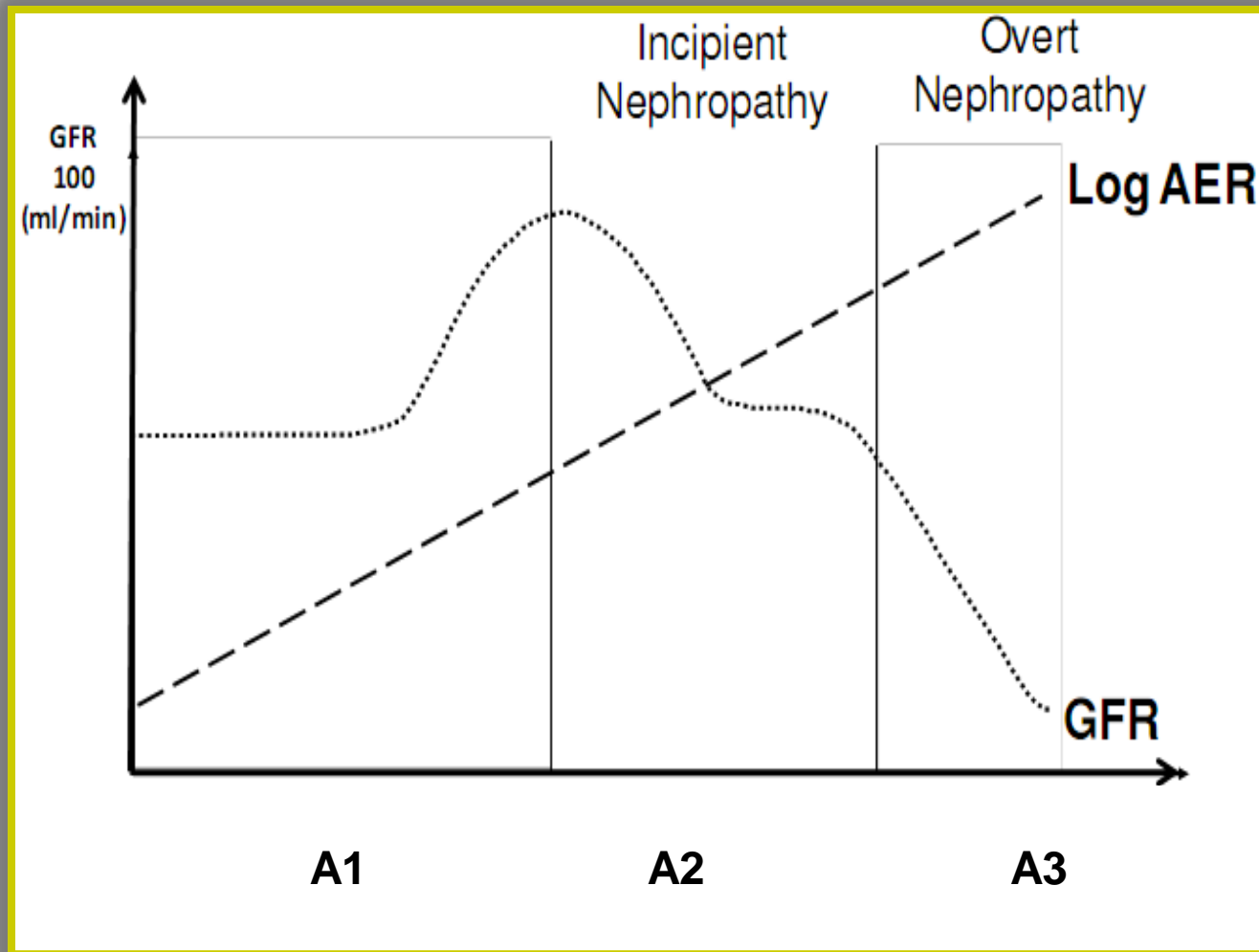
Number-tunneled vs Patient-centered?



“ Opportunities or Challenges “

Multi-Pathway Signal Blockade

The 5-Staged model of DKD

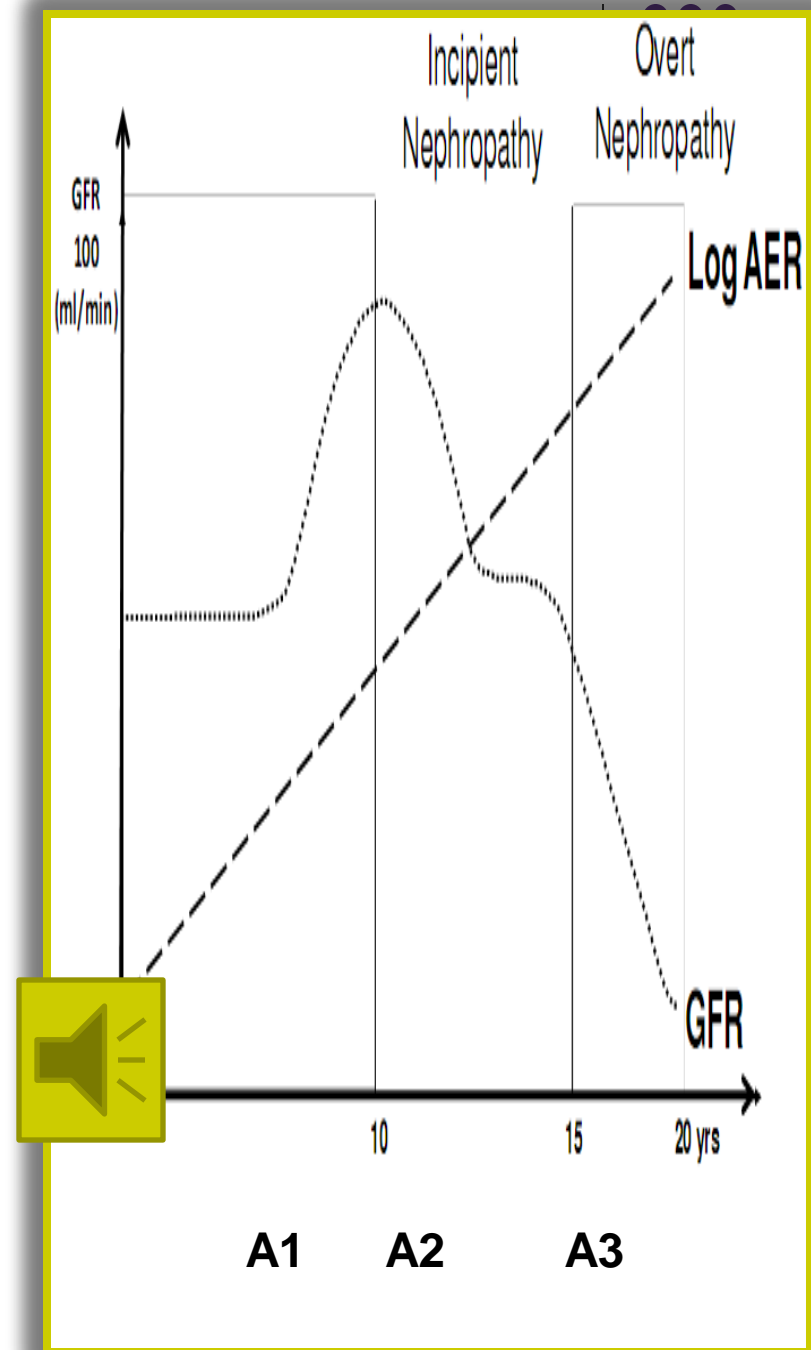


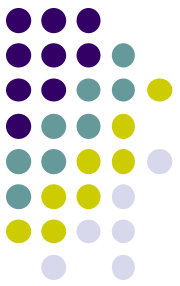
❑ Albuminuria (A2) “Micro”:

- ✓ Highly Variable:
(Ontarget)
Spontan.regression (30%).
- ✓ “Non-Proteinuric”
Phenotype (30%)/
RIACE (55% >>> F/CVD)
- ✓ Low Specificity:
Competing risk
(MACE & MAKE)
- ✓ Renal Endpoint?
(ME Molitch et al.
KI 2014)

❑ Albuminuria (A1) “Normo”:

- ✓ High Normal UAER:
Increased risk of
MACE/MAKE!
(Babazono et al.
Diabetes Care 2009)





(ME Molitch et al., KI 2014)
(Fox et al., Lancet 2012)
(de Boer et al.,
Diab Care 2009)

Cr-Based eGFR

U-shaped Mortality Curve

☐ Low eGFR:

- ✓ CVD + Renal Mortality(1)

☐ High eGFR

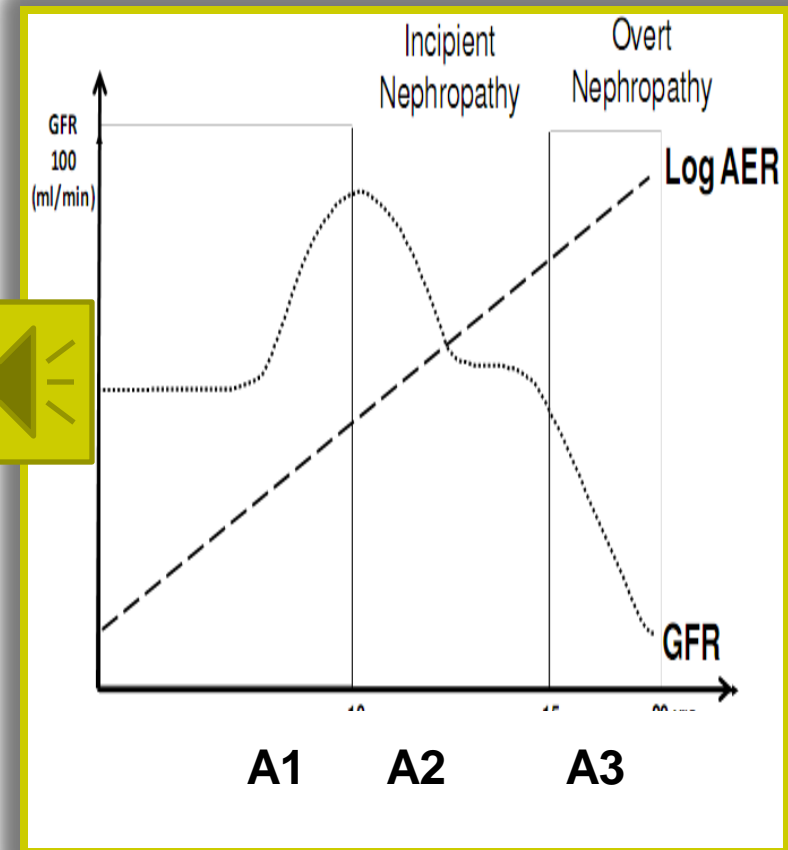
(Hyperfiltration):

- ✓ CVD Mortality(2)

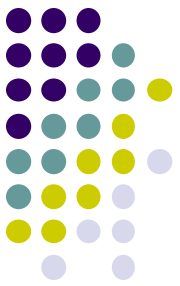
Cyst.C-Based eGFR

Better predicts

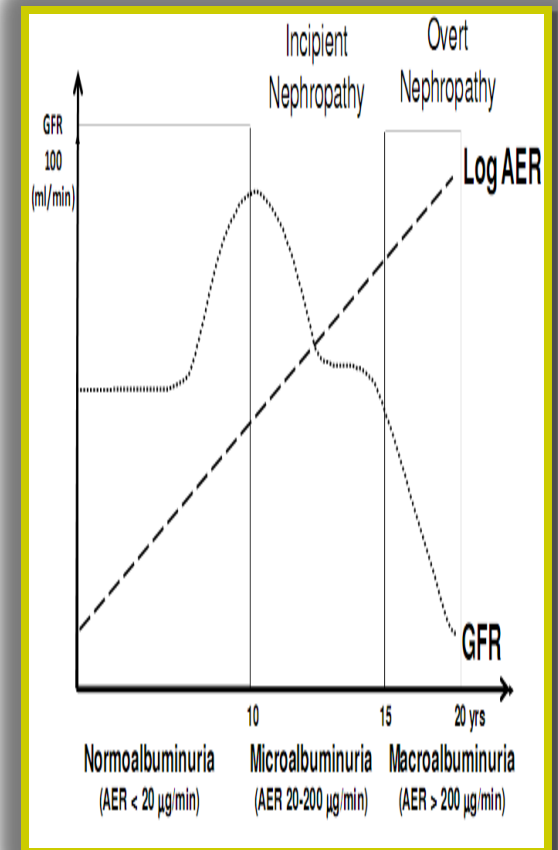
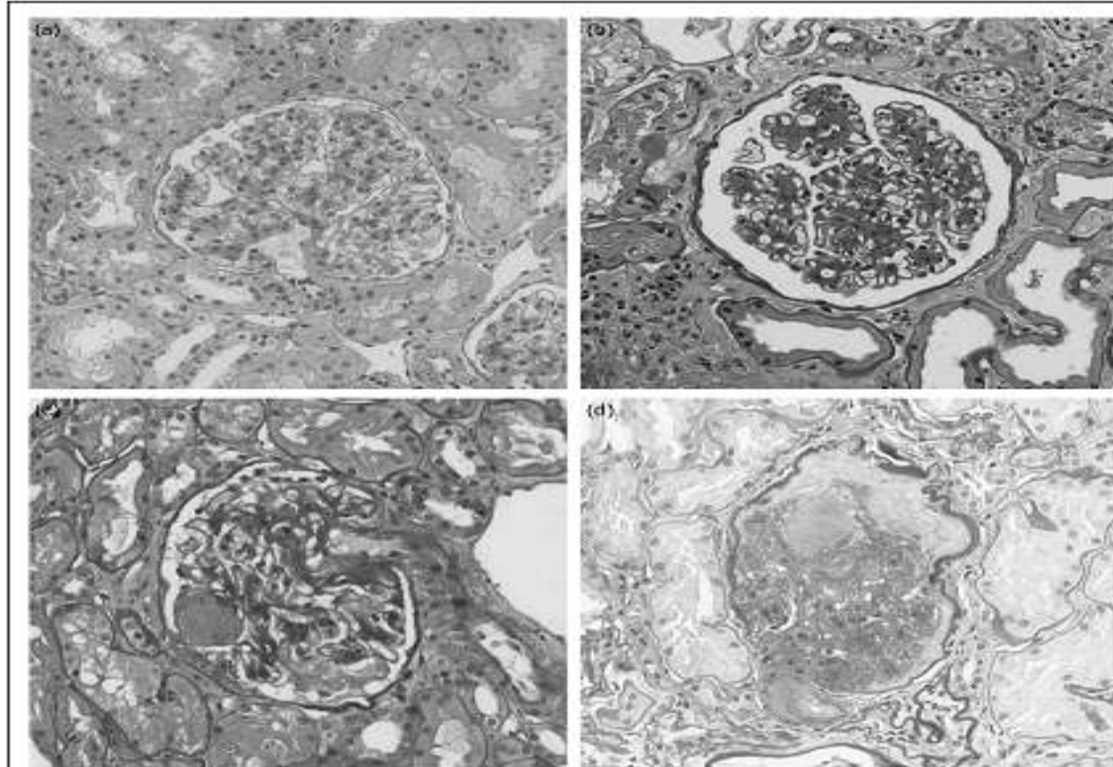
- ✓ death & prog. to
ESRD(3)



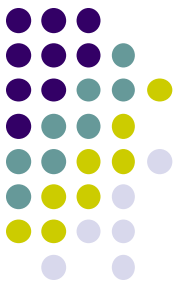
Biomarker? Functional vs Structural



(RPS Classif. 2010)



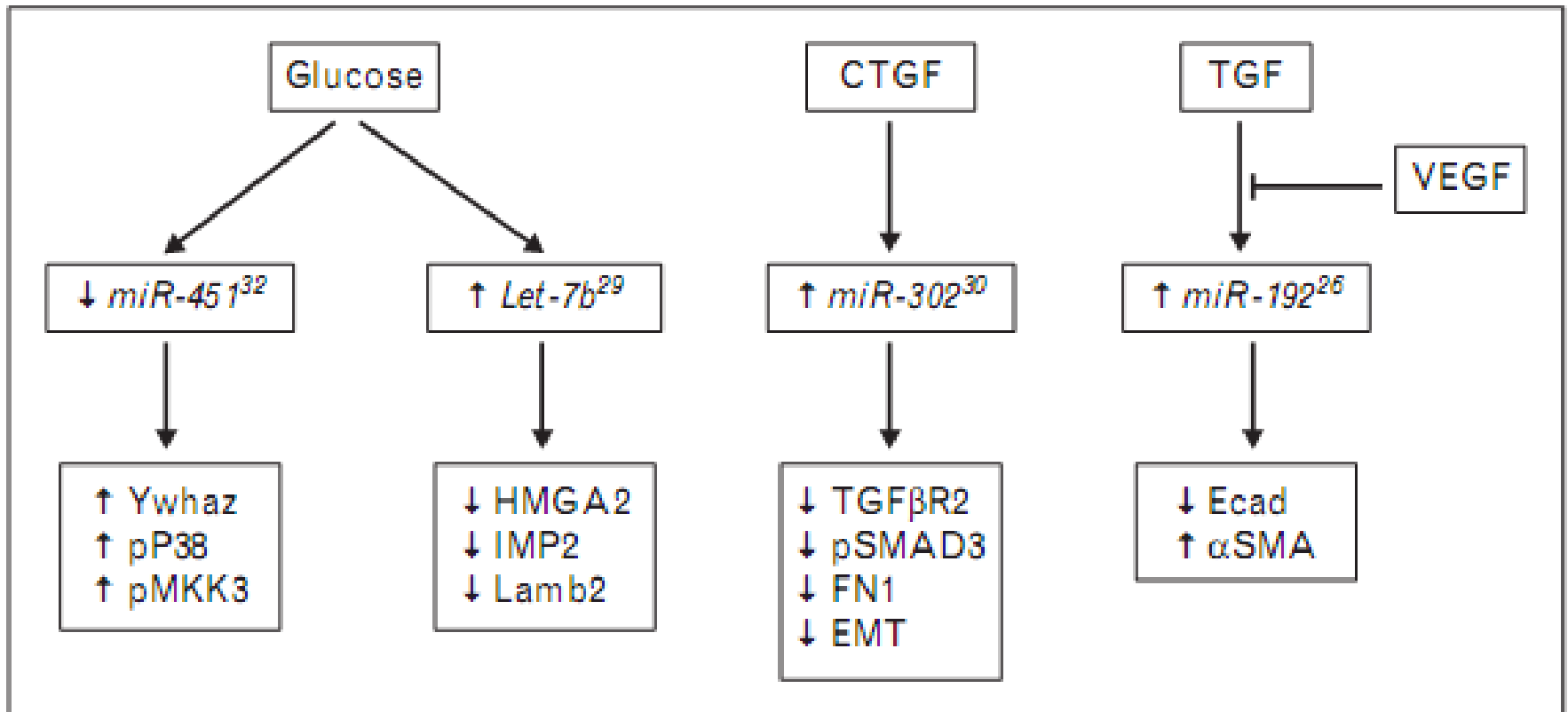
In search of new Biomarkers... “Epigenetics”



Where are we in diabetic nephropathy: microRNAs

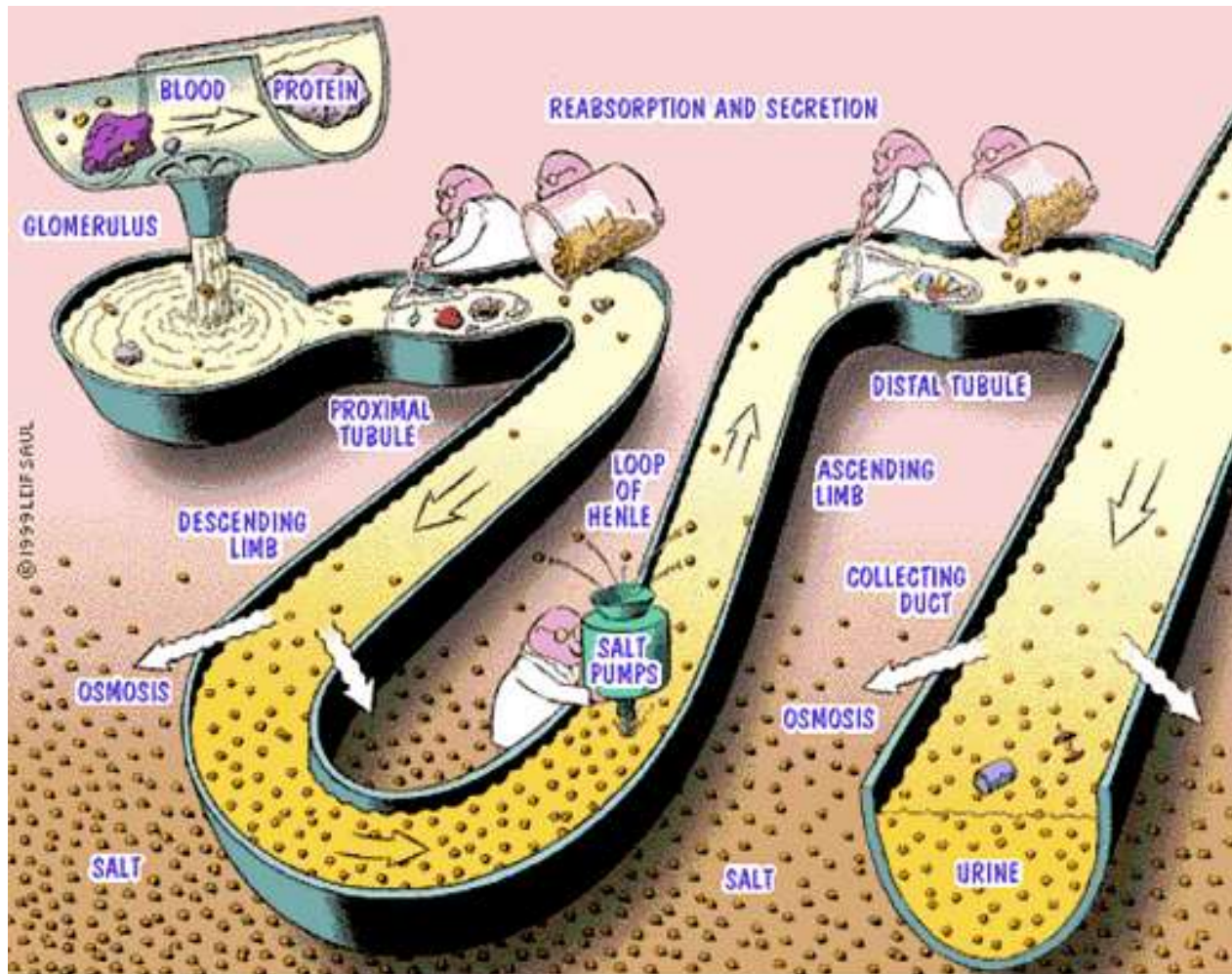
Aaron McClelland, Shinji Hagiwara, and Phillip Kantharidis

Curr Opin Nephrol Hypertens 2014,



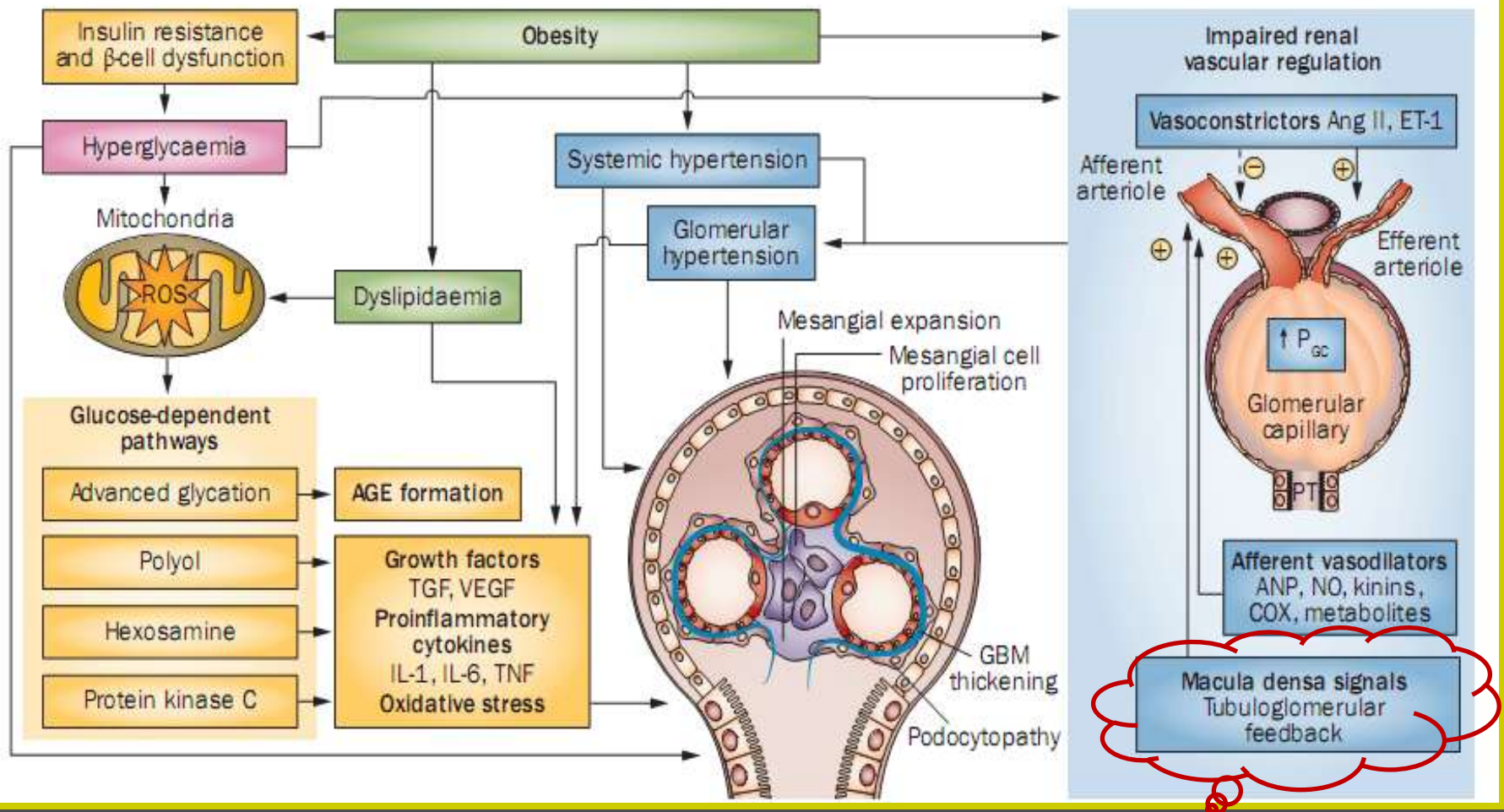
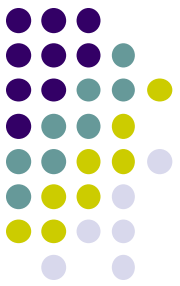
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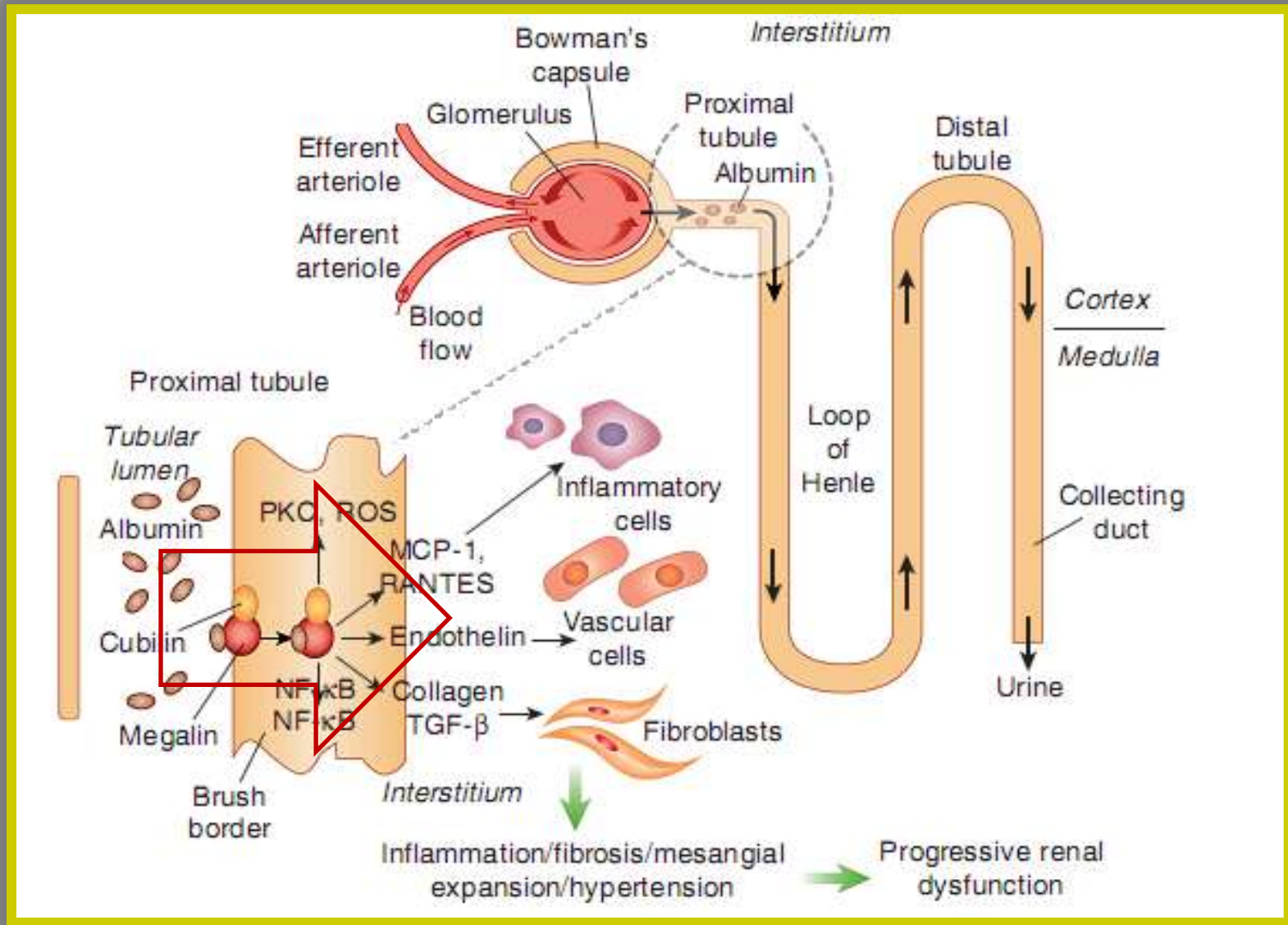
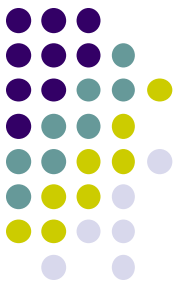


“Glomerulo”/centric DN

“TubuloGlomerular DKD”



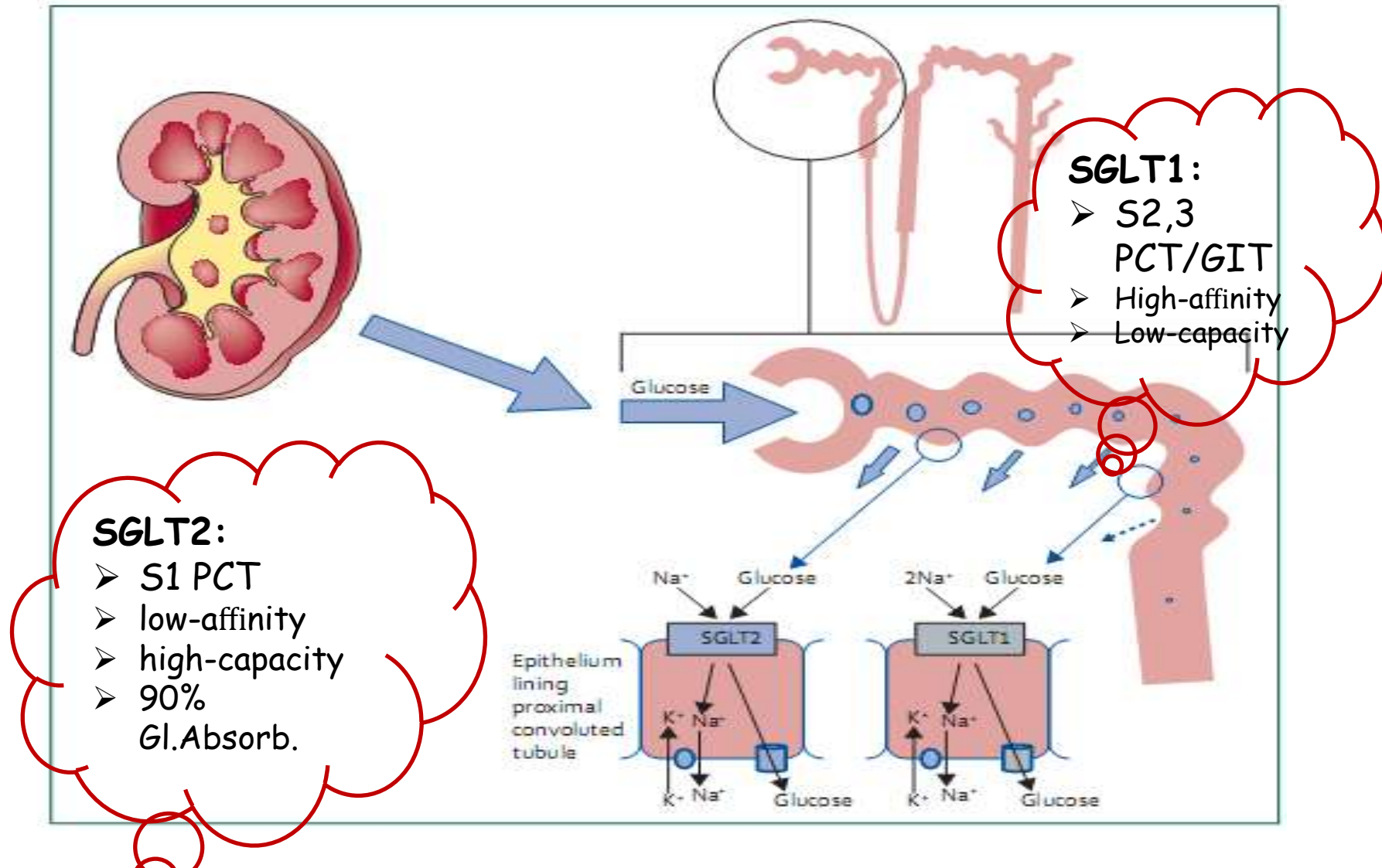
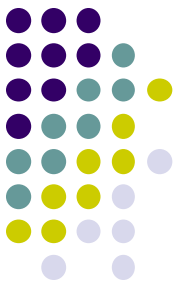
Albuminuria: “The Holy Grail “?



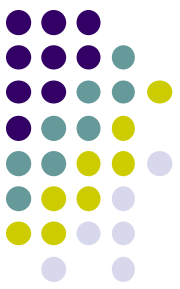
TubuloGlomerular Feedback: “ Cross Talks “?

“ Cross Talks “?

Tahrani et al. Lancet 2011



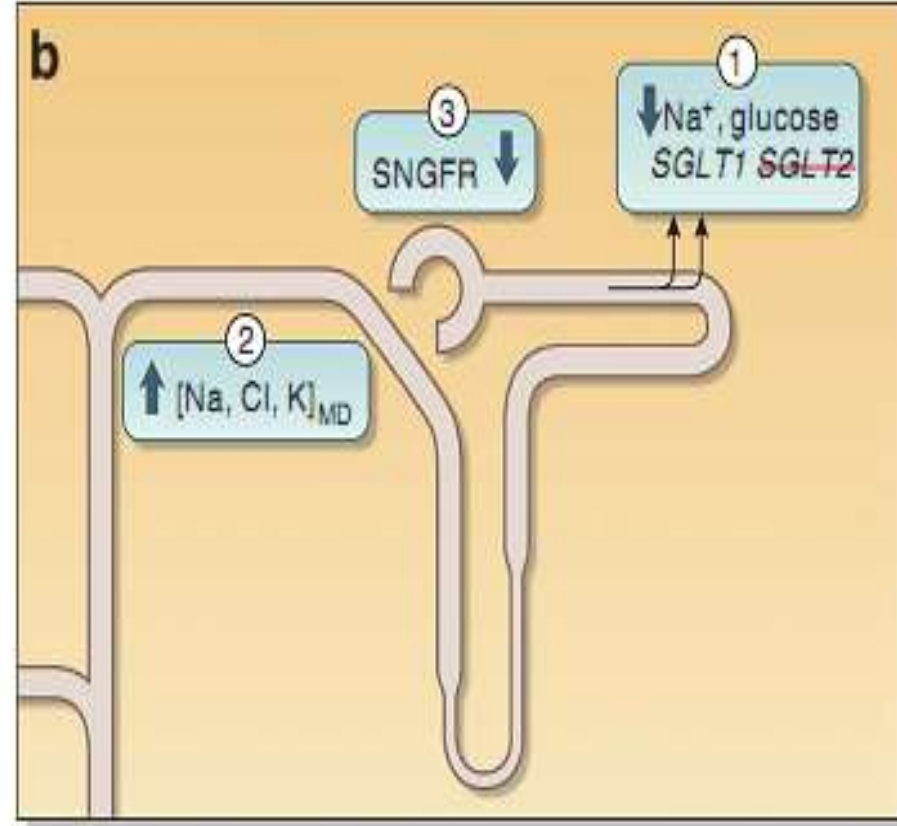
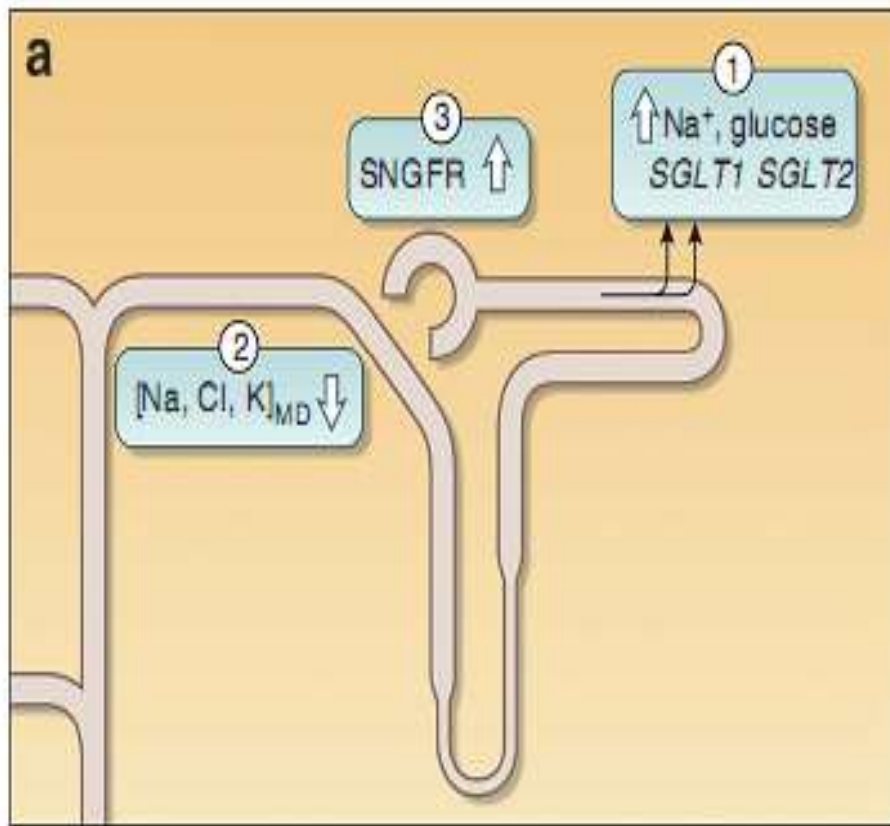
TubuloGlomerular Feedback: “Salt Paradox”?



Sodium–glucose linked transporter-2 inhibitors:
potential for renoprotection beyond blood glucose
lowering?

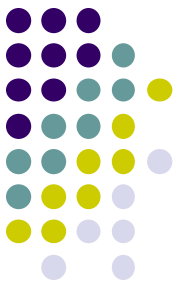
Richard Gilbert KI 2013

Richard E. Gilbert¹

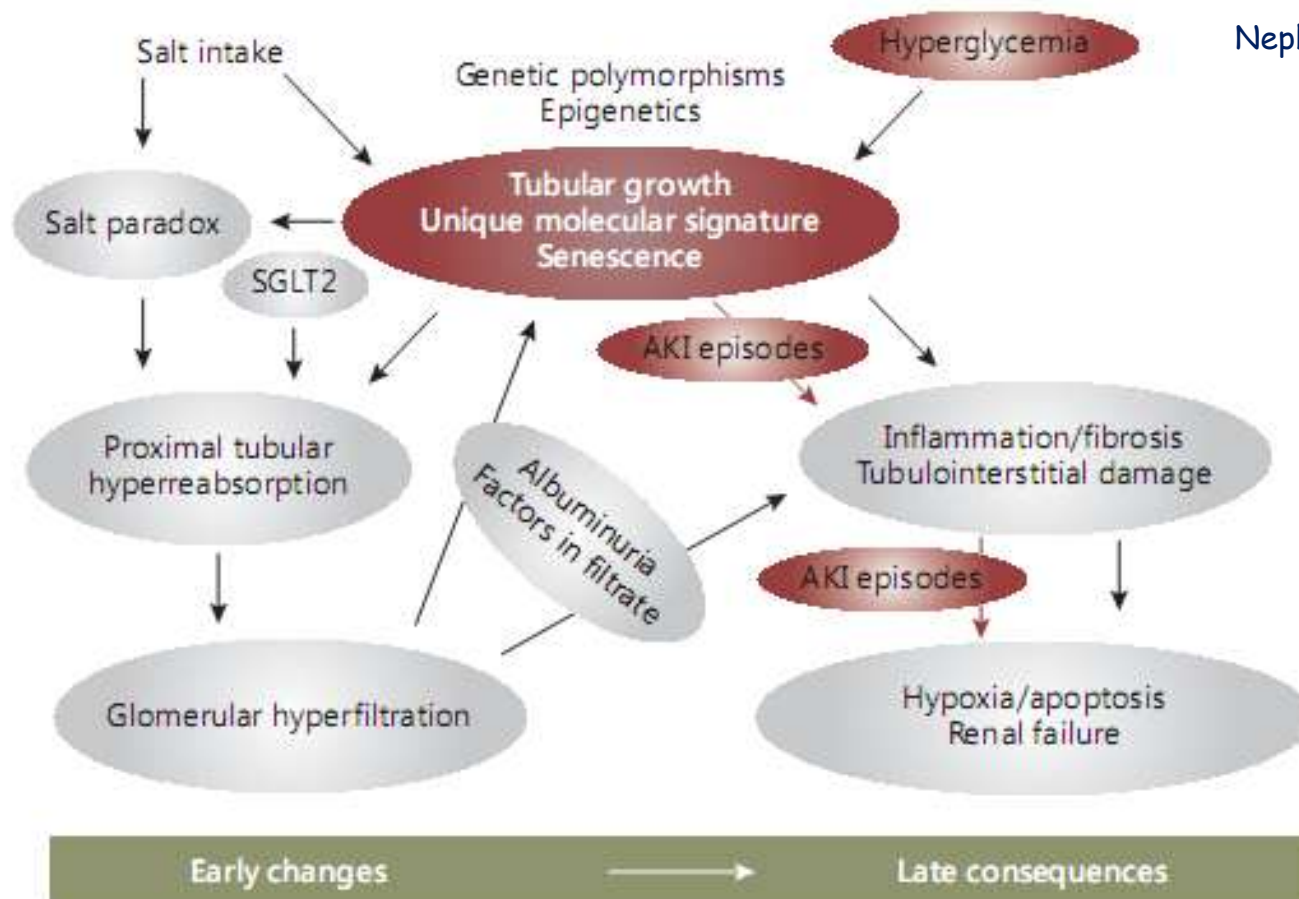


“Tubulo”/centric DN

“Tubulopathic DKD ?”



Volker Vallon
Nephron Clin Pract
2014

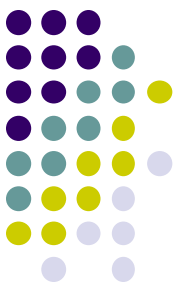




“From Bench to Bedside “ One-size-fits-all Approach?

 “Conventional Paradigm “
Number-tunneled vs Patient-centered?

 “Opportunities or Challenges “
Multi-Pathway Signal Blockade

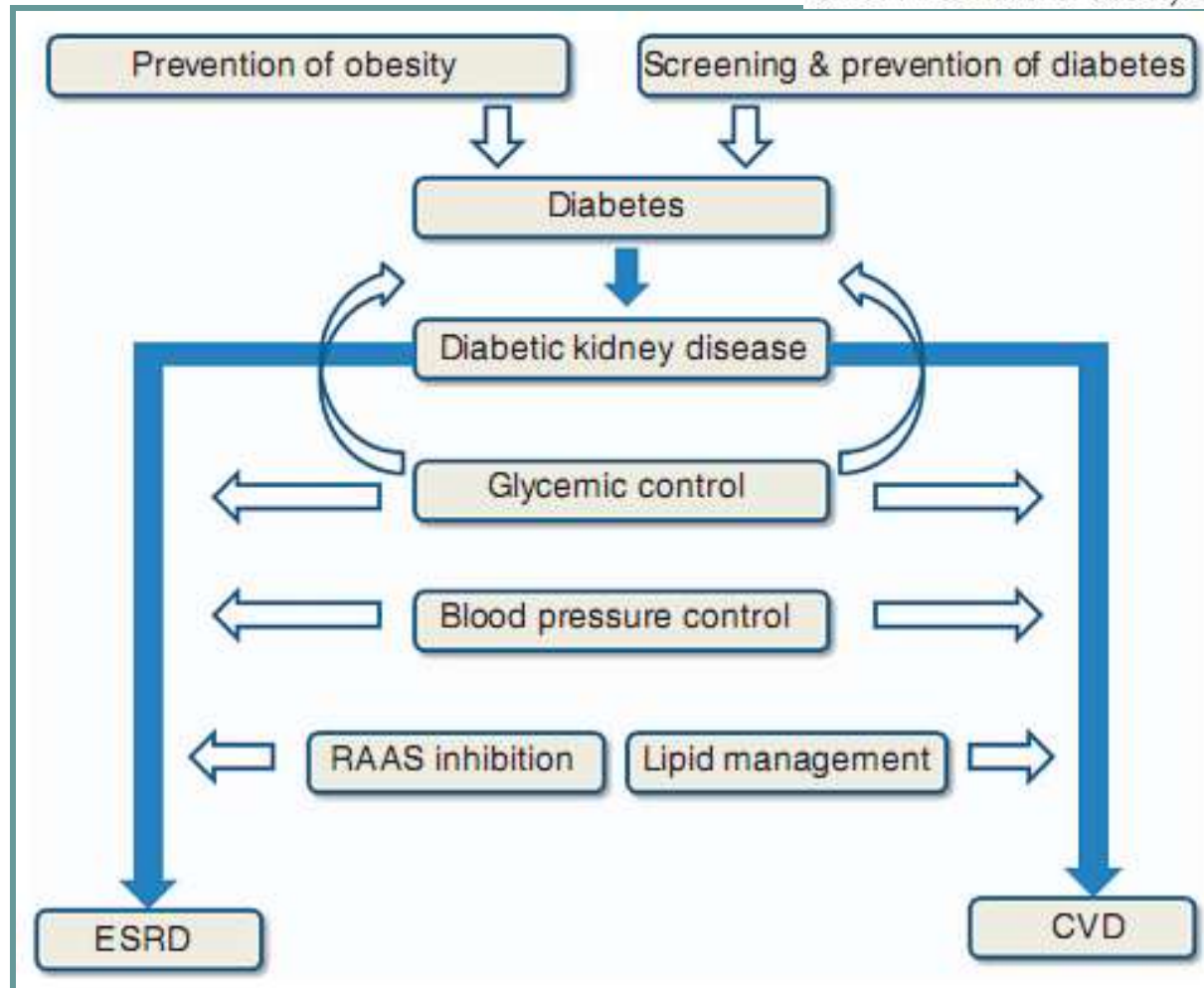


Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes

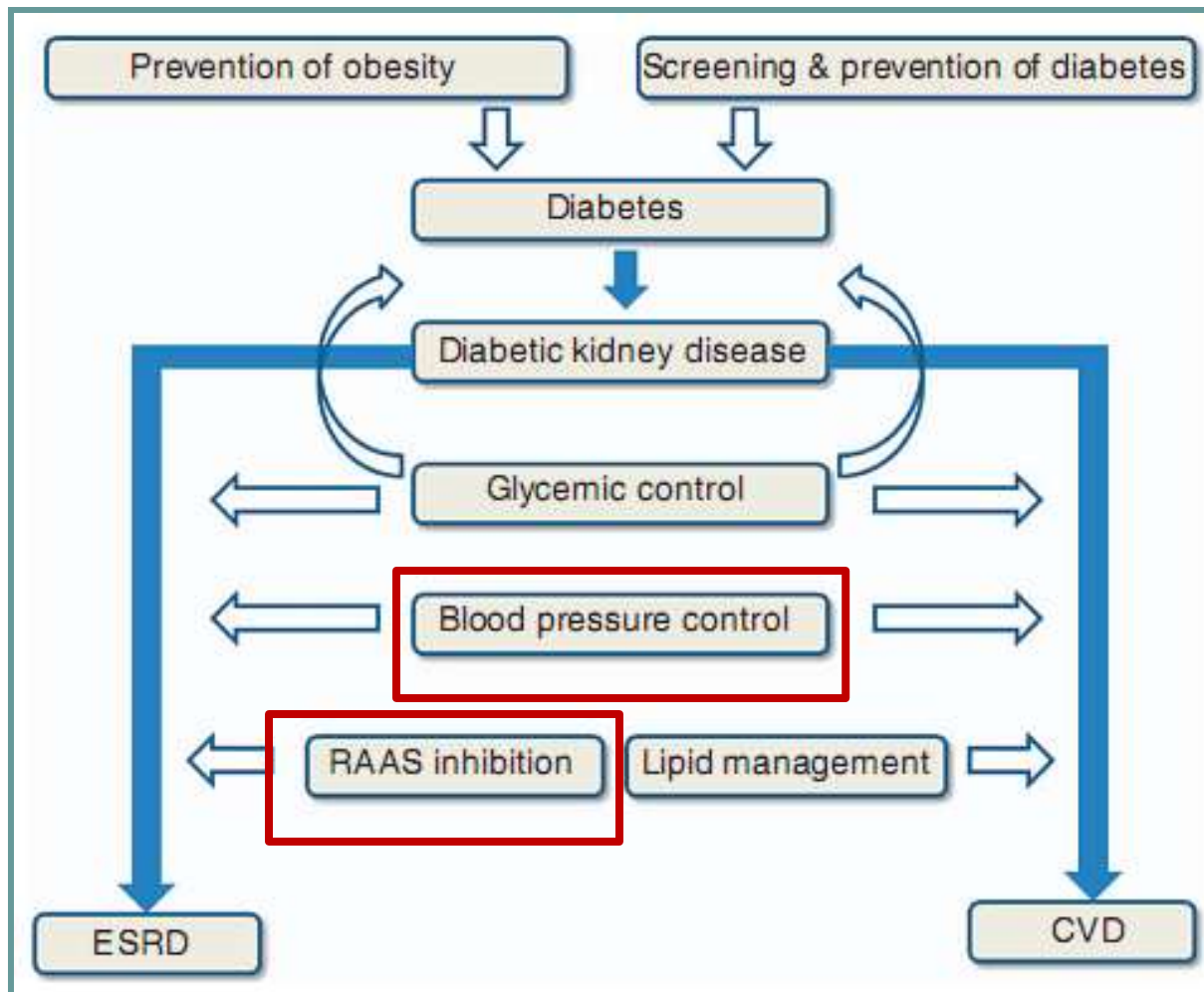
Mark E. Molitch¹, Amanda I. Adler², Allan Flyvbjerg³, Robert G. Nelson⁴, Wing-Yee So⁵, Christoph Wanner⁶, Bertram L. Kasiske⁷, David C. Wheeler⁸, Dick de Zeeuw⁹ and Carl E. Mogensen¹⁰

<http://www.kidney-international.org>

© 2014 International Society of Nephrology



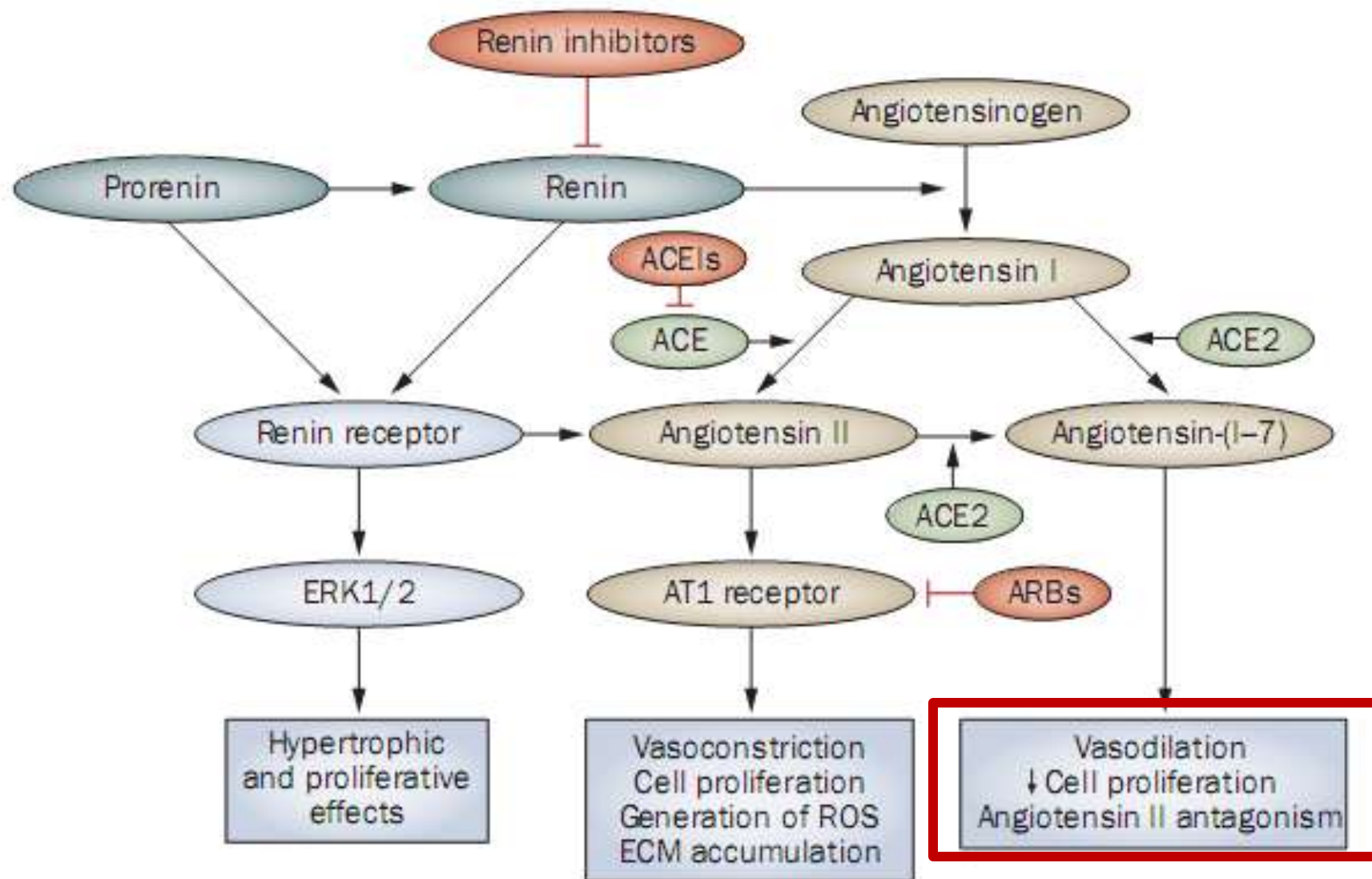
Conventional wisdom:



New pharmacological treatments for improving renal outcomes in diabetes

Anne-Emilie Declèves and Kumar Sharma

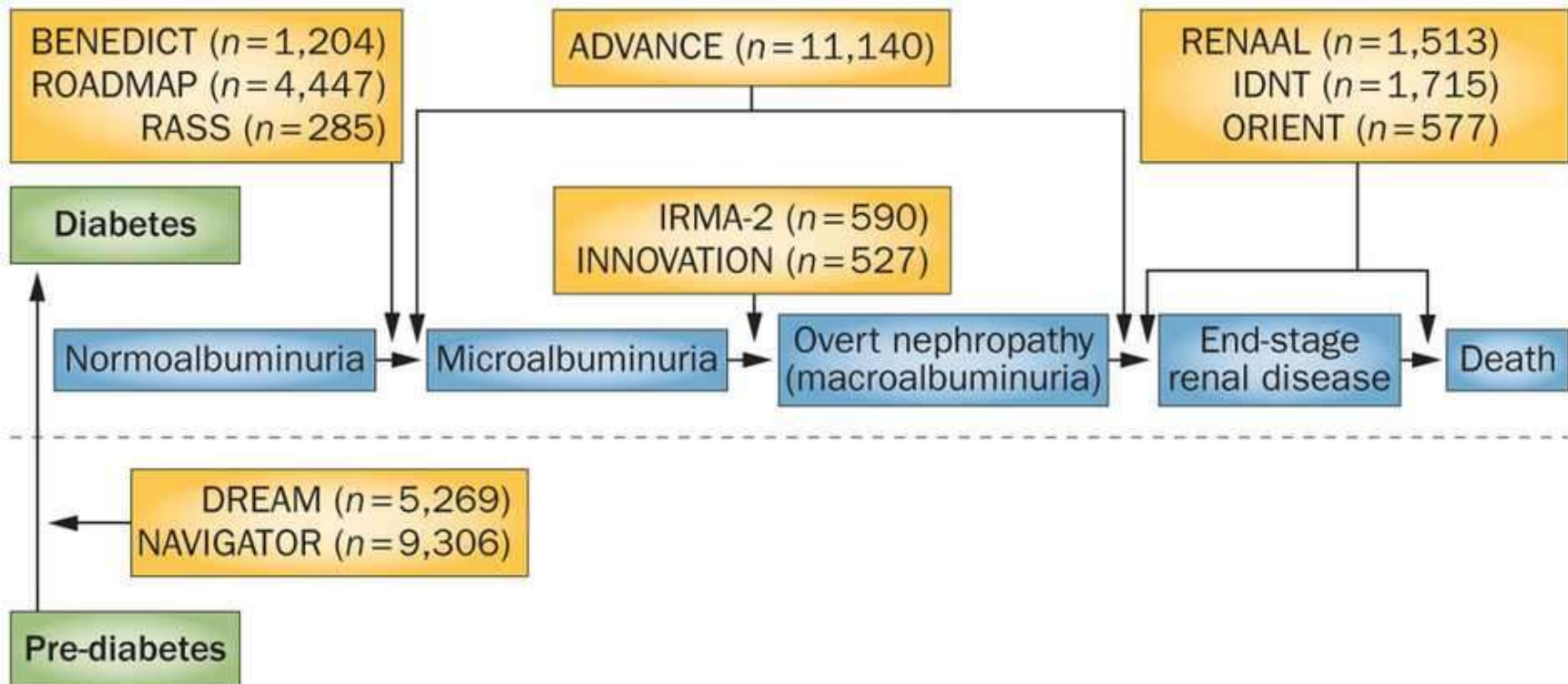
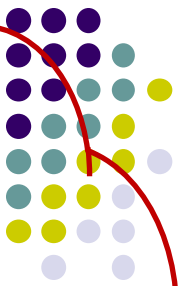
Nat. Rev. Nephrol. 6, 371–380 (2010);



RAAS Blockade: The Mantra ?

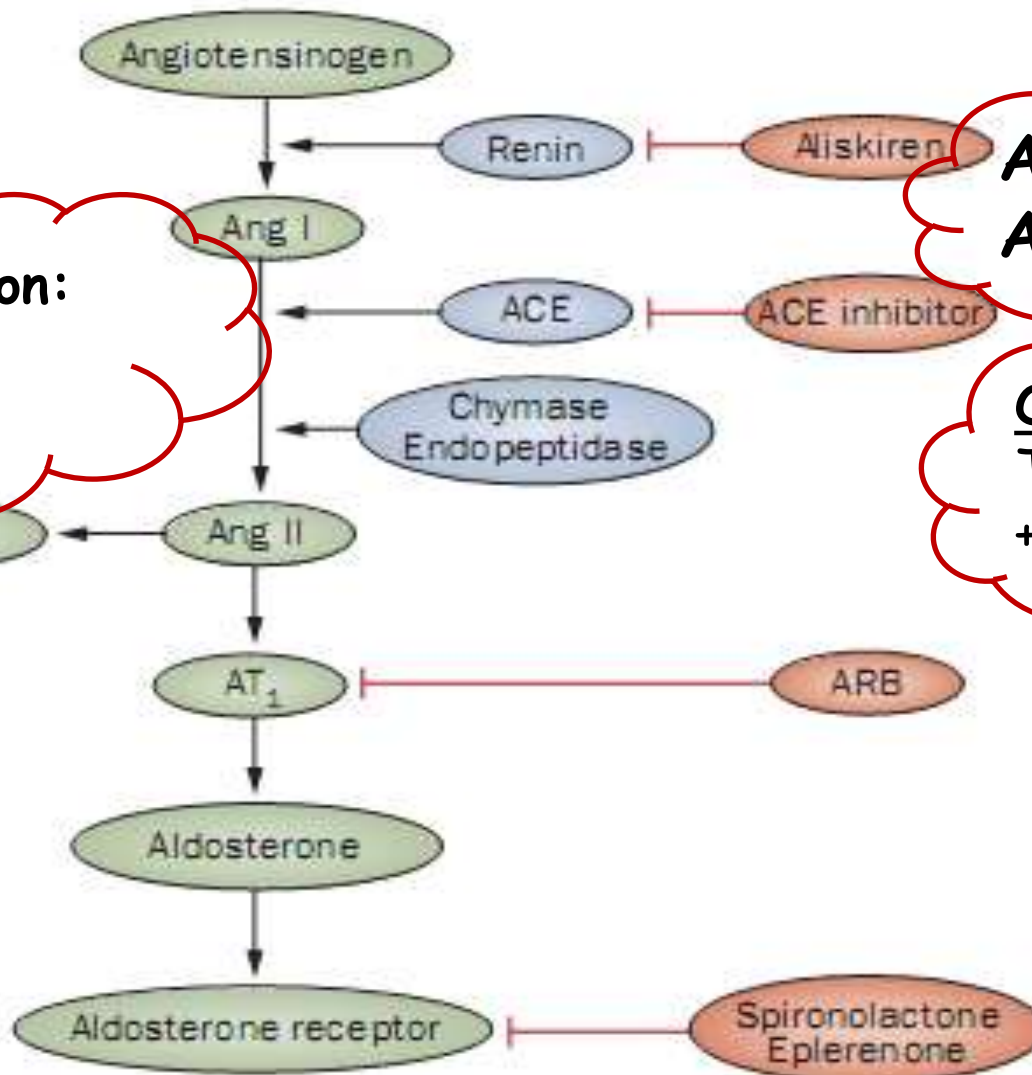
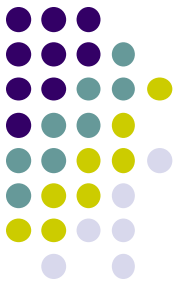
Sara Roscioni Nature Nephrology 2013

- ☐ Target Dose?
- ☐ Salt restriction
- ☐ Dual Blockade
- ☐ VDR Analogues



RAAS Blockade:

“Challenging the Dogma?”



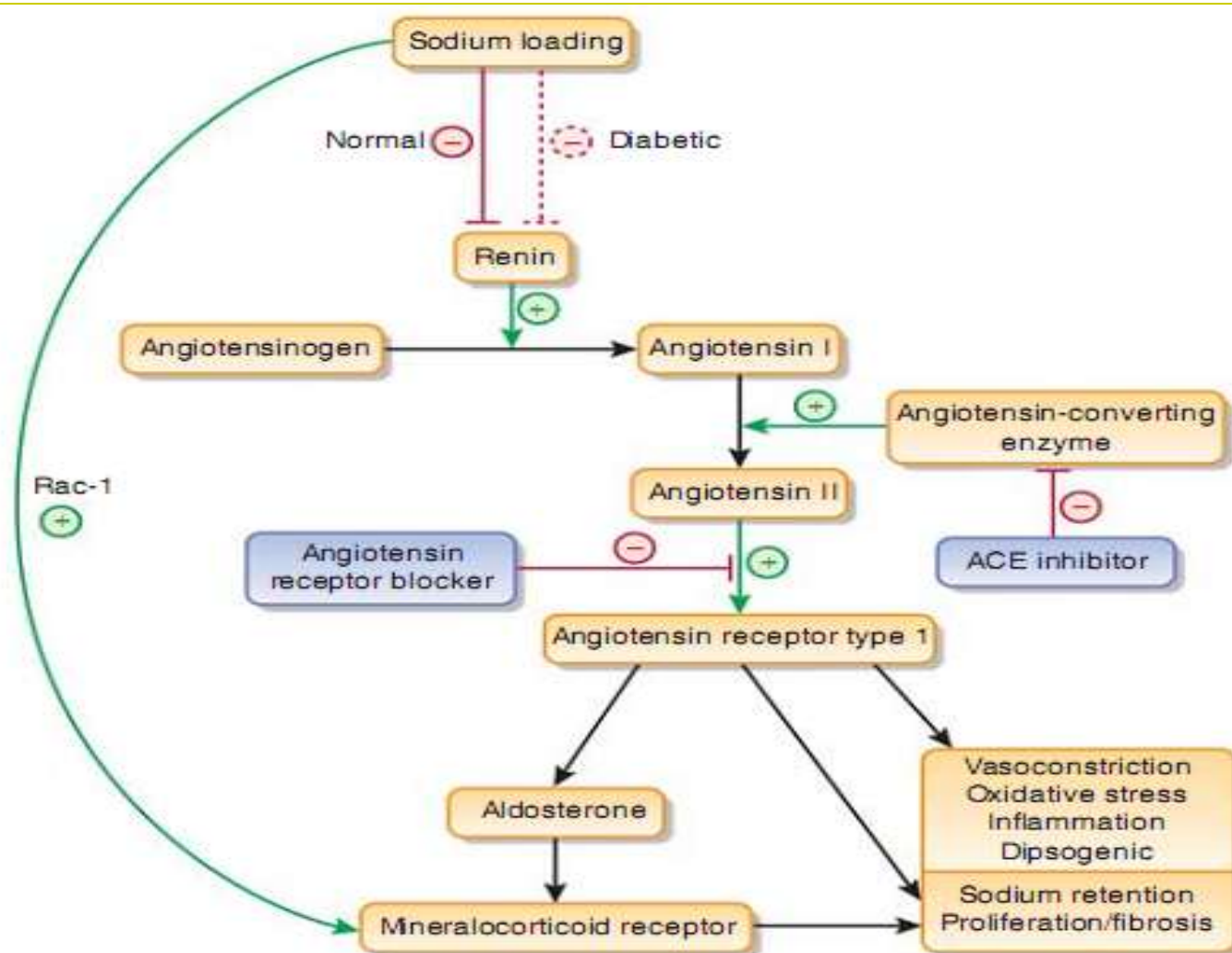
Va -Nephron:
Losartan+
Lisinopril

Altitude:
Aliskirin

OnTarget:
Telmisartan
+ Ramipril

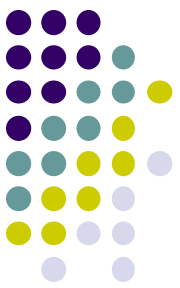
You Are What You Eat ?

“Salt Paradox”



RAAS Blockade:

Optimizing the response ?

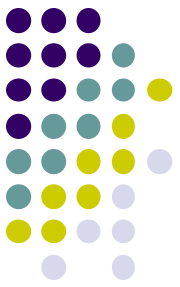


Improving the efficacy of RAAS blockade in patients with chronic kidney disease

Hiddo J. Lambers Heerspink, Martin H. de Borst, Stephan J. L. Bakker and Gerjan J. Navis

Outcome measures	Regular sodium diet (11 g NaCl per day)		Low sodium diet (6 g NaCl per day)	
	ACE inhibitor	ACE inhibitor plus ARB	ACE inhibitor	ACE inhibitor plus ARB
Systolic blood pressure (mmHg)	134 (128–140)	131 (125–137)	123 (127–119)*‡	121 (115–127)*‡
Proteinuria (g per day)	1.7 (1.3–1.1)	1.4 (1.1–1.9)*	0.9 (0.7–1.1)*‡	0.7 (0.5–0.9)*‡§
Serum potassium (mmol/l)	4.6 (0.1)	4.6 (0.1)	4.7 (0.1)*	5.0 (0.1)*‡§
Creatinine clearance (ml/min)	72 (62–84)	74 (65–84)	66 (57–76)*‡	61 (53–70)*‡

* $P < 0.01$ vs an ACE inhibitor plus regular sodium diet. ‡ $P < 0.01$ vs an ACE inhibitor plus an ARB and regular sodium diet. § $P < 0.01$ vs an ACE inhibitor and low sodium diet. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; RAAS, renin-angiotensin-aldosterone system. Data derived from Slagman et al.⁴⁷



RAAS BLOCKADE: The Holy Grail? “Opposite View”

❑ “Imperfect ?”

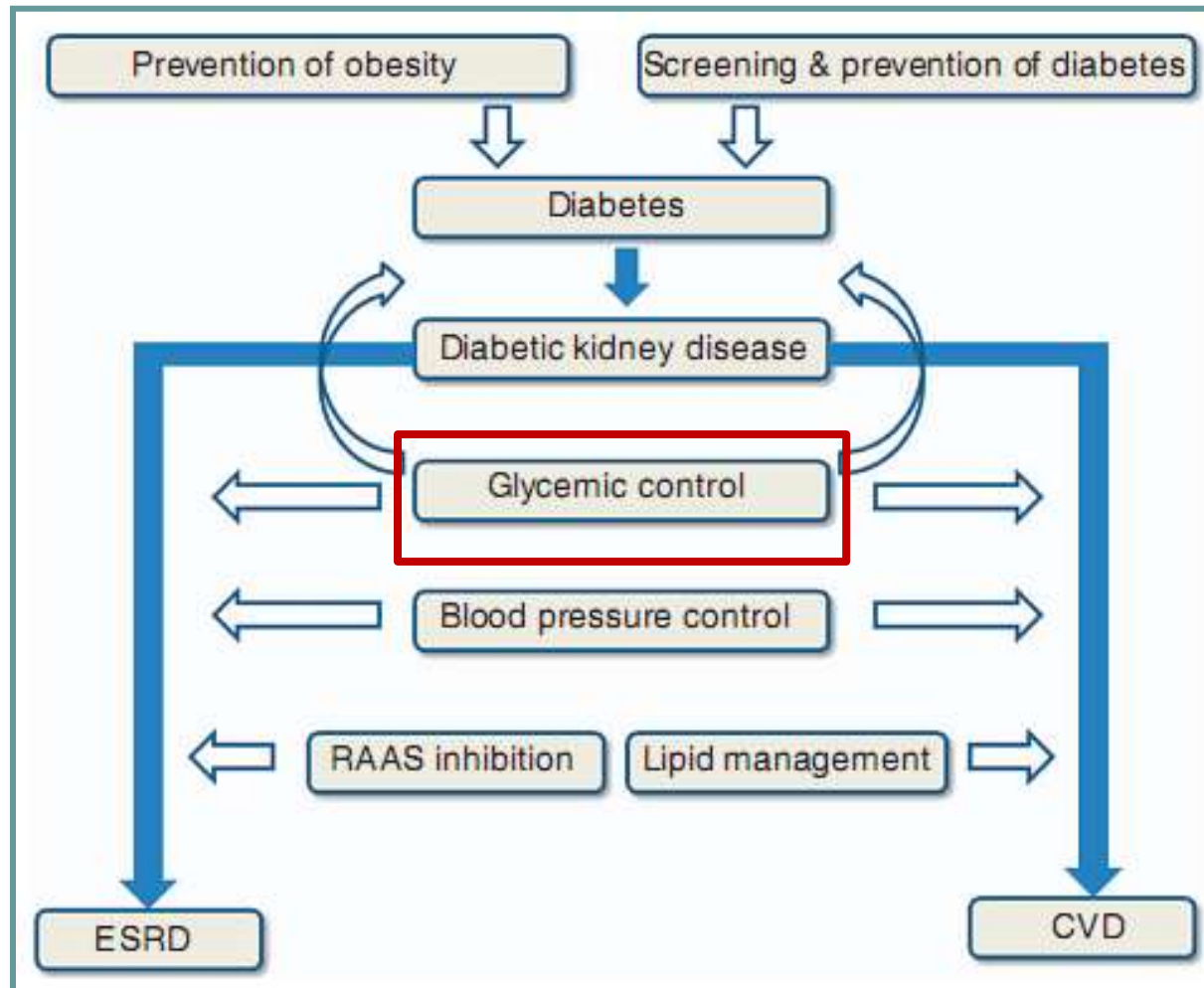
- ✓ Breakthrough/Escape “phenomenon”
- ✓ Non-proteinuric Progressors
- ✓ Ischemic Nephropathy (25-30%).

Macaulay Onuigbo
Nephron Clin Pract
2011

❑ “Deleterious ?” :

- ✓ Early: AKI “s” !!
(Ontarget)/)(Roadmap)
- ✓ Late: SORO-ESRD !!
(Maculay Ongabli/Nahas)

Conventional wisdom: “Challenging the Dogma?”





Dysglycemia ?

☐ **AKI.**

☐ **CKD.**

Glycemic Control:

“Monitoring= eAG”



☐ **Glycated Haemoglobin?**

- ✓ Longer duration
- ✓ Surrogate used in major Trials

☐ **Glycated Albumin?**

☐ **Fructosamine (AlbF)?**

☐ **Contin. Gluc. Monitoring(CGM)**

(Marijn Speeckaert et al., ERPB, NDT, 2014)

Glycemic Control: “Monitoring”



HBA1c!!



You Are What You Eat ?

“ Sweet Debate ”



NEWS IN FOCUS

290 | NATURE | VOL 513 | 18 SEPTEMBER 2014



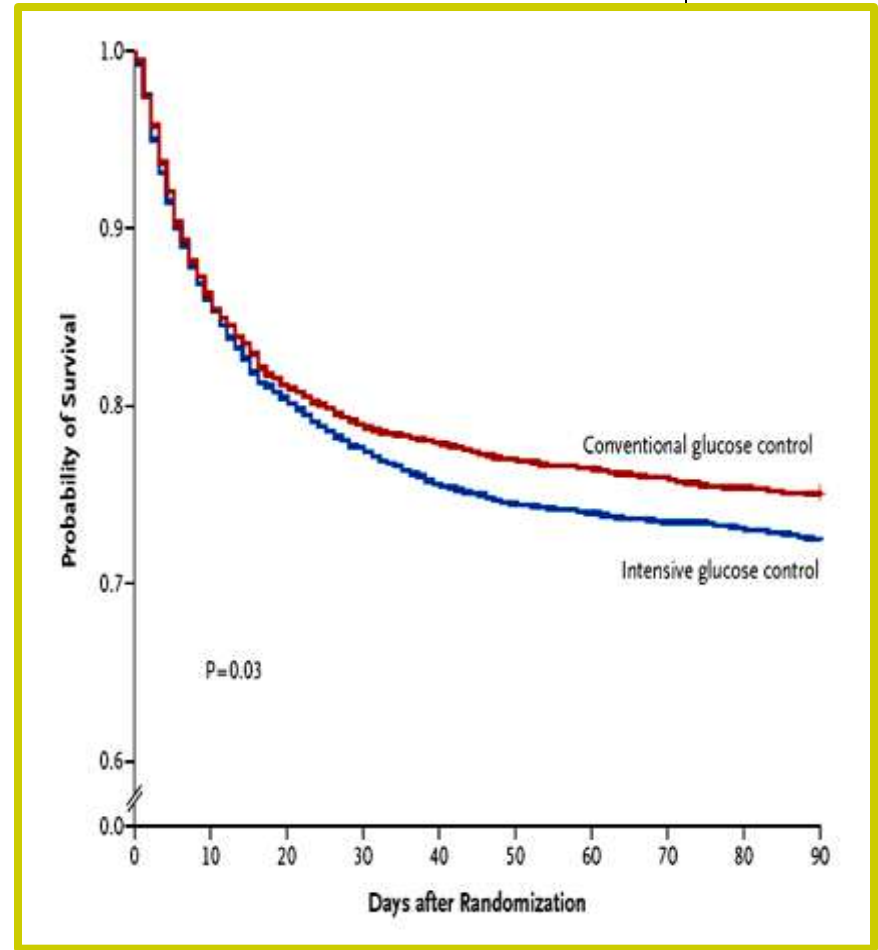
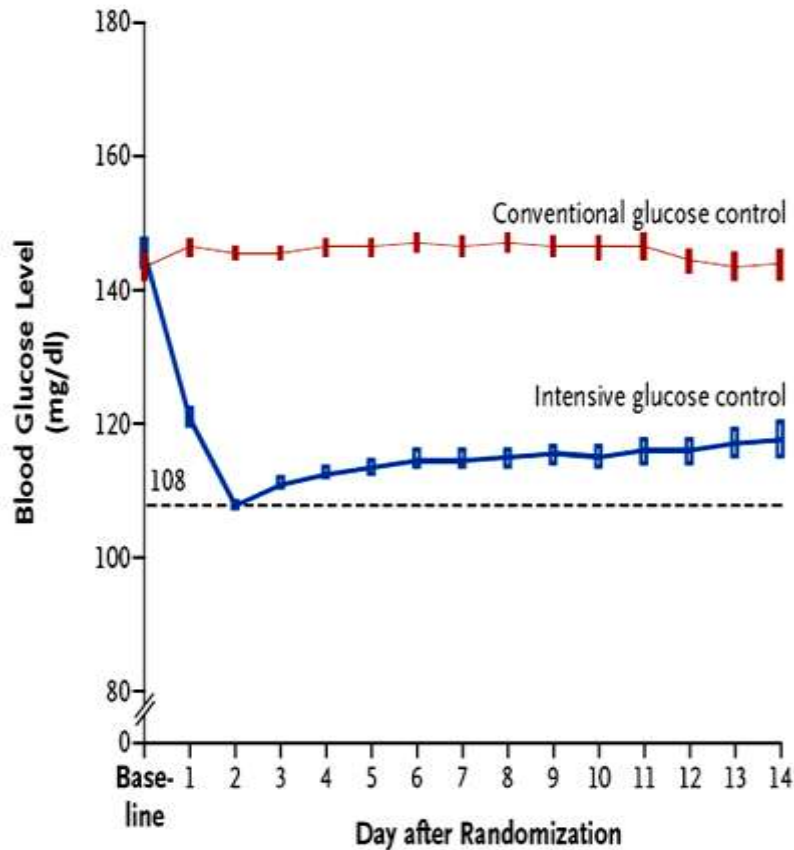
Soft drinks are just some of the many products that use artificial sweeteners.

NUTRITION

Sugar substitutes linked to obesity

Artificial sweetener seems to change gut microbiome.

Glycemic Control: in AKI: “NICE SUGAR”



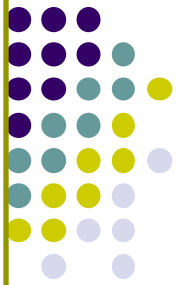
90 day mortality: IIT:(27.5%), CIT: (24.9%)

Absolute mortality difference: 2.6%

Odds ratio for death with IIT was 1.14.

Glycemic Control: CKD

“Act Now or Pay Later”



□ Mortality & HbA1c

✓ U-shaped curve

HbA1c () 6.5% – 9 %

➤ CKD-ND

(Arch Intern Med 2011)

➤ CKD5-HD

(Diabetes care 2012)

➤ CKD5-PD

DOPPS (JASN 2011) & (KI 2012)

✓ **HbA1c > 8% pretransplant**

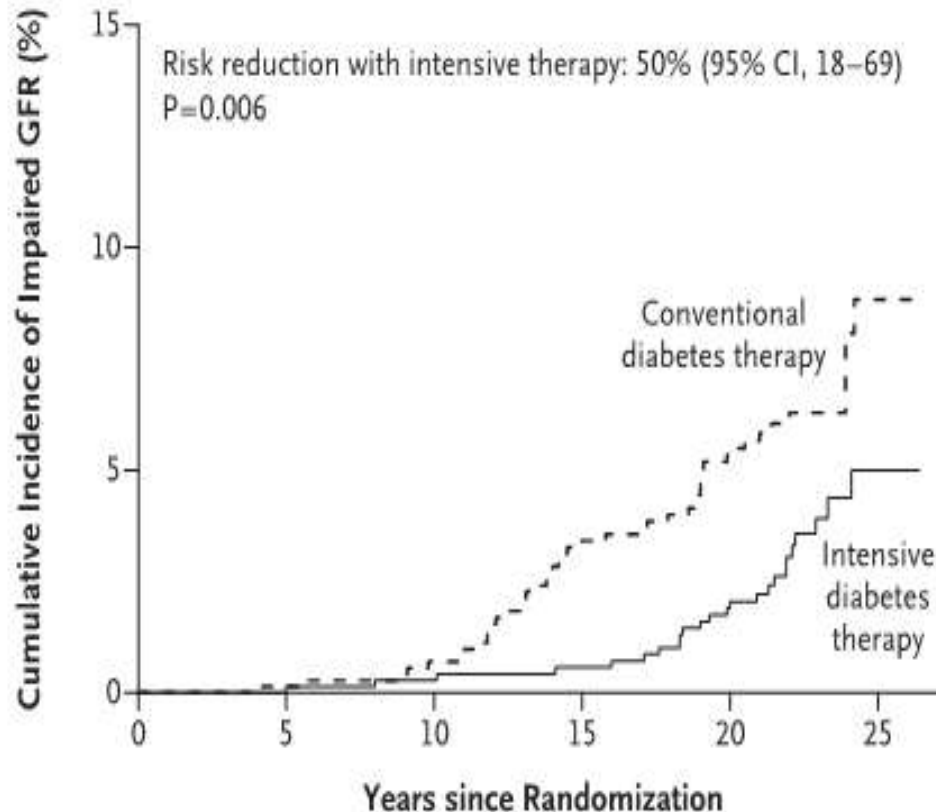
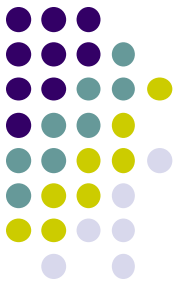
Tx ??

(Molnar et al. Diabetes Care 2011)

Observational
studies

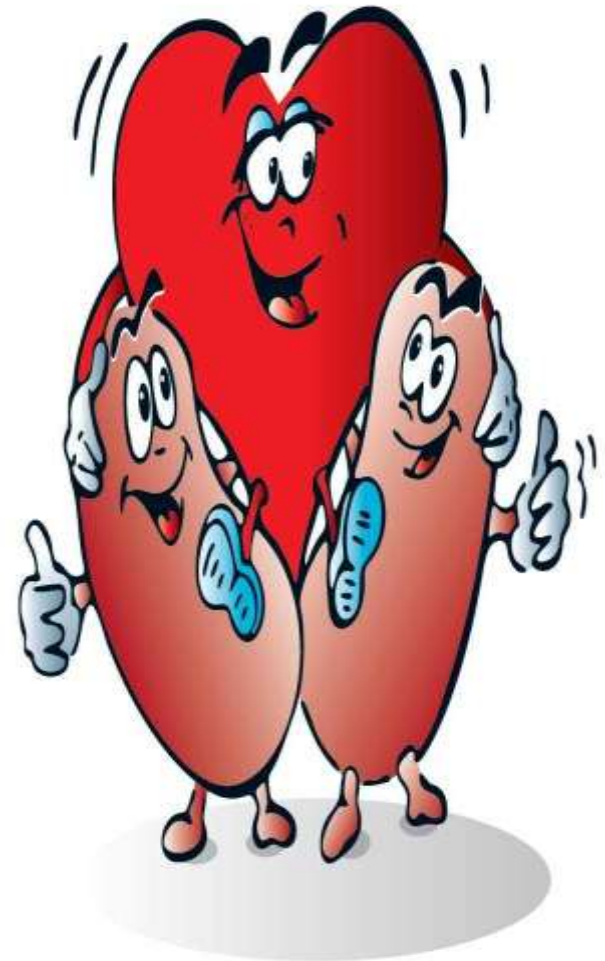
Glycemic Control:

“Act Now >> T1DM: DCCT/EDIC”



No. at Risk

Intensive therapy	711	704	684	672	619	108
Conventional therapy	730	719	697	657	594	90

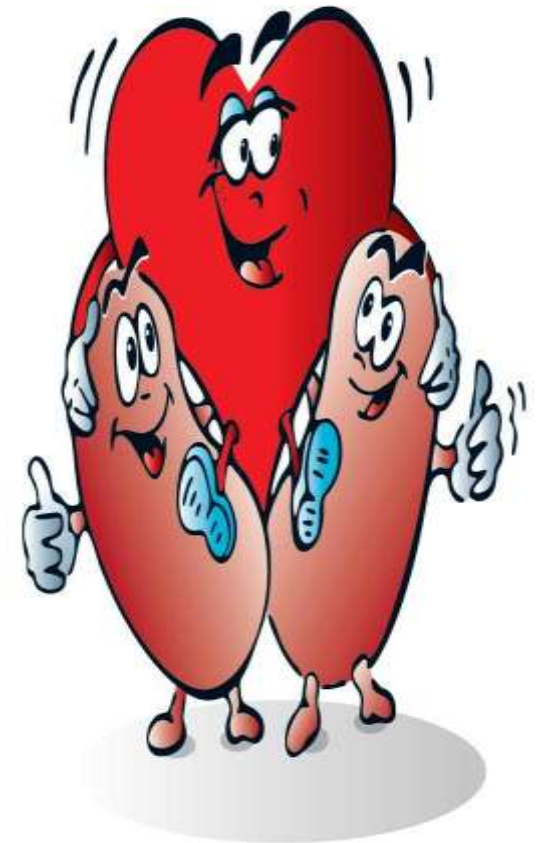
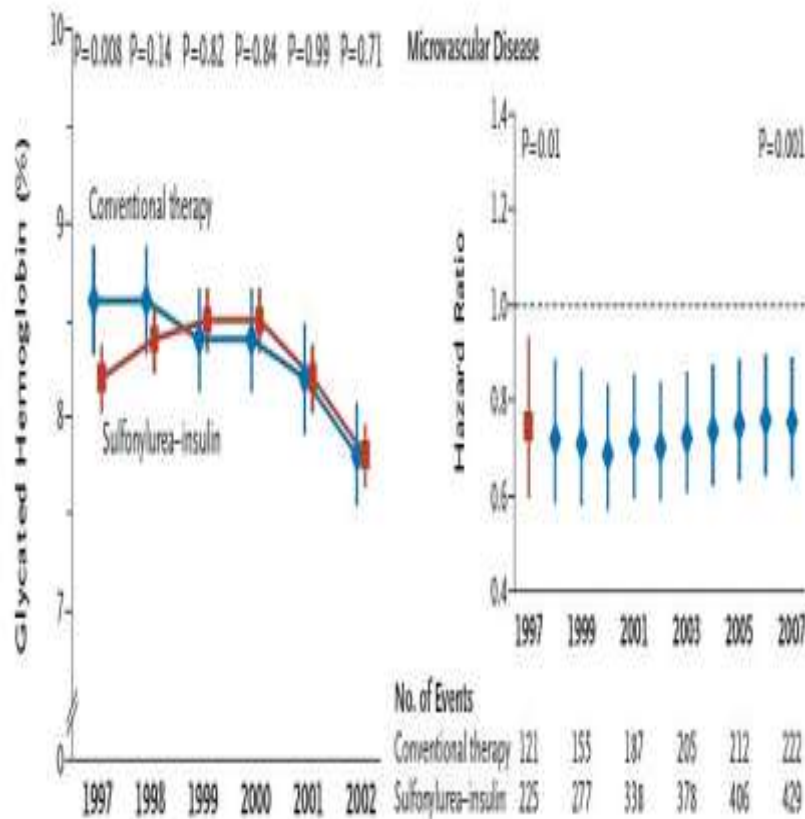


Glycemic Control:

“Act Now >> T2DM: UKPDS”

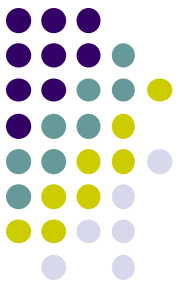


Holman NEJM 2008



“Intensive Glycemic Control”:

Do the Benefits justify the Risks ?



Study	HbA1c		Outcome of albuminuria or renal events
	Intensive treatment	Conventional treatment	
ACCORD ^[45]	6.4% vs 7.6%		21% ↓ in onset of microalbuminuria 32% ↓ in progression to macroalbuminuria
ADVANCE ^[46]	6.5% vs 7.3%		9% ↓ in onset of microalbuminuria 30% ↓ in progression to macroalbuminuria 21% ↓ in renal events New onset macroalbuminuria Doubling of serum Cr Kidney replacement therapy Death due to kidney disease
VADT ^[47]	6.9% vs 8.4%		32% ↓ in progression from normal to microalbuminuria or macroalbuminuria 37% ↓ in progression from normal to microalbuminuria to macroalbuminuria 34% ↓ in any increase in albuminuria

**Posthoc
Subgroup
Analysis**

**Soft
Surrogates**

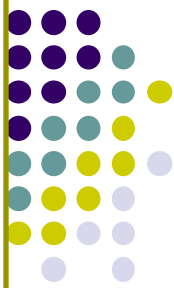
**Excess
ALL-Cause/
CVD mortality**

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular disease: Preterax and Diamicon MR Controlled Evaluation; VADT: Veterans Affairs Diabetes Trial.

Munehro et al., WJD, 2014

Glycemic Control:

“Act Now or Pay Later”



□ Act Now !

- **Metabolic Memory?**
- ✓ **(UKPDS)**
- **Legacy effect?**
- ✓ **(DCCT/EDIC)**
- **microRNAs?**



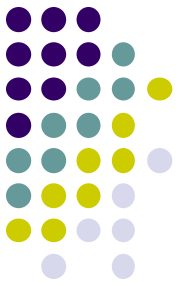
□ Pay Later !

- **Burnt out DKD ?**
- ✓ **(ACCORD).**
- ✓ **(ADVANCE/ON).**
- ✓ **(VADT).**

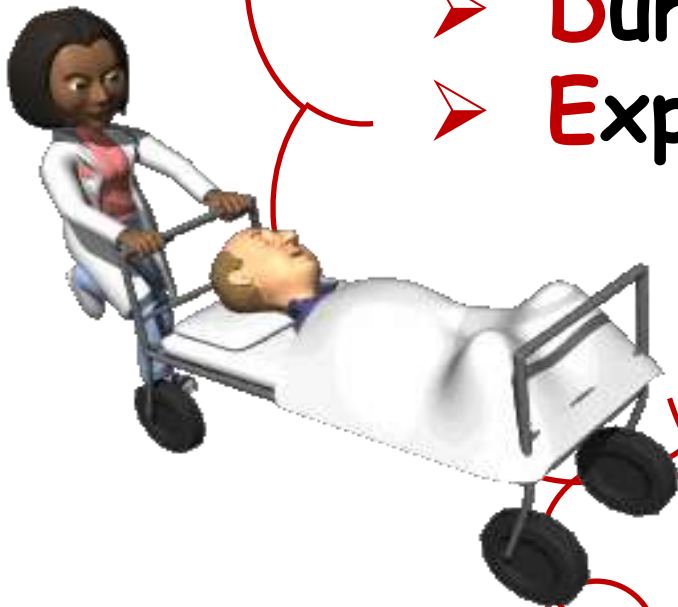


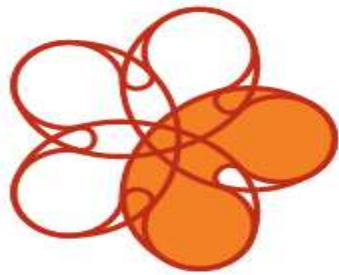
ADA/AHA position statement 2014:

Skyler (Diabetes Care 2009)



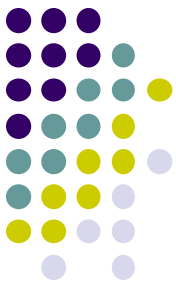
- **A**ge
- **B**.W
- **C**omplication
- **D**uration
- **E**xpectancy





National Kidney Foundation®

KDOQI



KDOQI Diabetes Guideline: 2012 Update

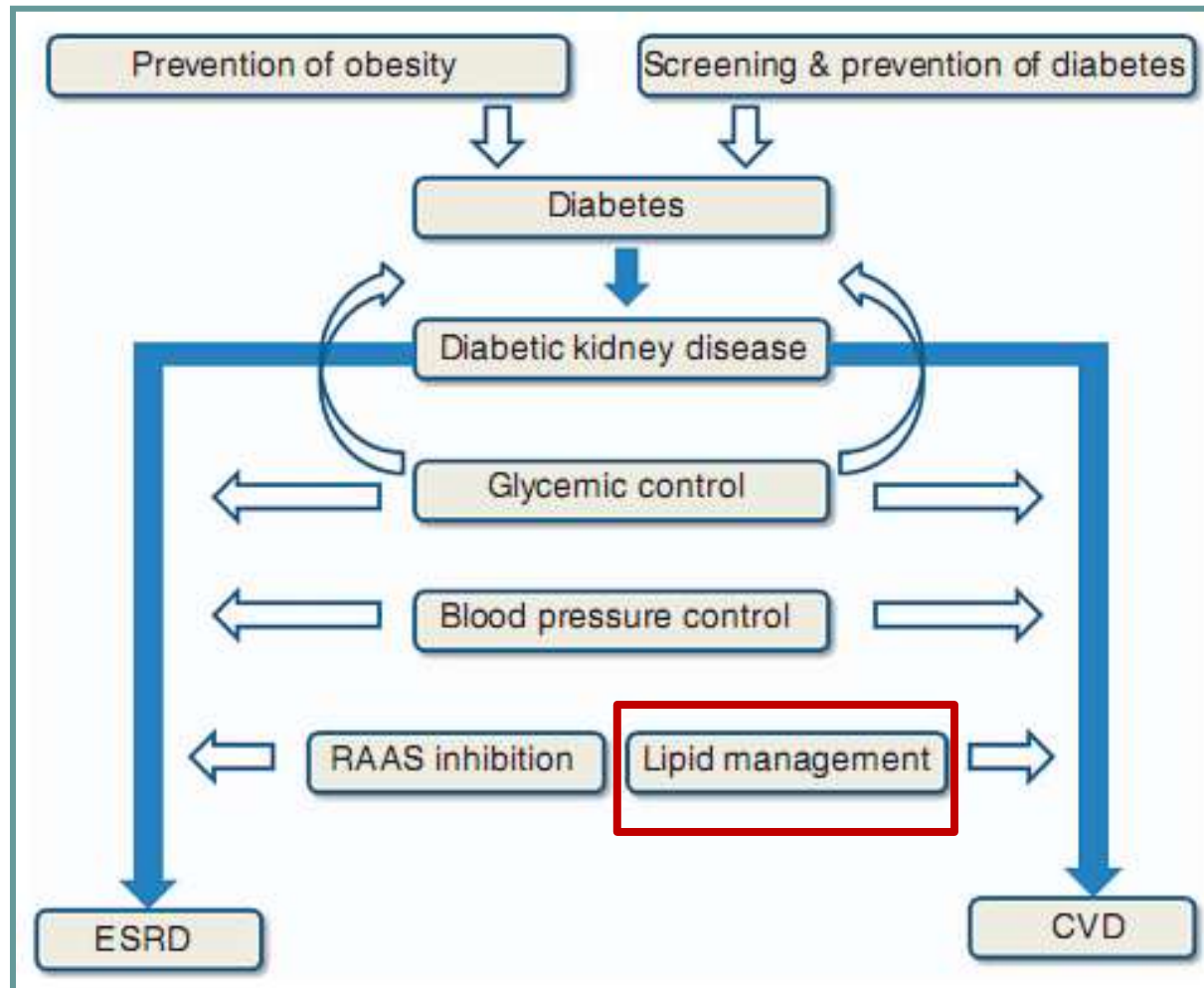
AJKD

		Chronic kidney disease stage (dialysis not included)	
Class	Drug	3A 45-59 mL/min	3B 30-44 mL/min
Biguanides	Metformin	No dose adjustment ¹	Half-dose ¹
Sulfonylureas	Glibenclamide	No dose adjustment	
	Glipizide		
	Gliclazide	No dose adjustment ²	
	Glimepiride	Initiate at low dose (1mg)	Initiate at low dose (1mg) ²
Meglitinide analogues	Nateglinide	No dose adjustment	Initiate at low dose (60mg)
	Repaglinide		Initiate at low dose (0.5mg)
Thiazolidinediones	Pioglitazone	No dose adjustment ³	
Alpha-glucosidase inhibitors	Acarbose	No dose adjustment	Avoid
	Miglitol		
Dipeptidyl Peptidase-4 Inhibitors	Sitagliptin	No dose adjustment ⁴	50mg/day ⁴
	Vildagliptin		
	Saxagliptin		
	Alogliptin		12.5mg/day ⁴
	Linagliptin	No dose adjustment	

Metformin:
Reappraisal

SGLT2i:
New Promises
“Crescedence”⁰

Conventional wisdom: “Challenging the Dogma?”



(1 B) : CKD-ND & RTx : Statin +/- Ezetimibe.

KDOQI Diabetes Guideline: 2012 Update

AJKD



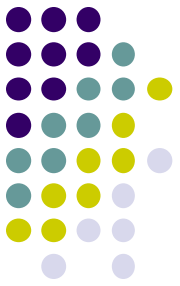
MACE
reduction
Not
Renal
endpoints

Posthoc
Subgroup
Analysis

Negative outcomes:
4D
AURORA
SHARP

CKD-D: Non-Start Non-Stop Policy

"Not to initiate" (1B) !

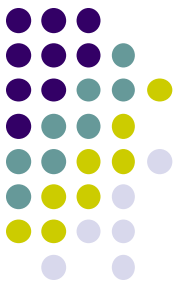


 **“ From Bench to Bedside “**
One-size-fits-all Approach?

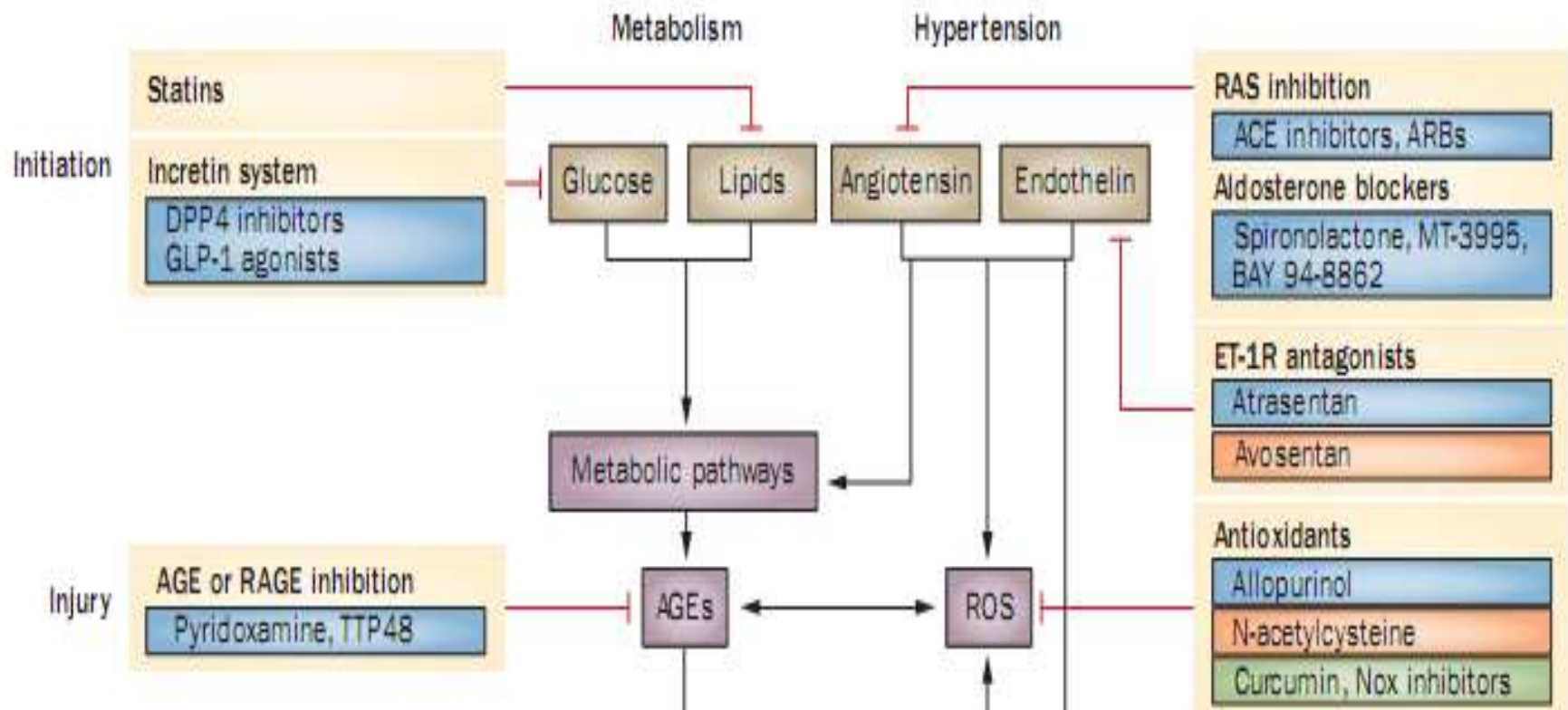
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Number-tunneled vs Patient-centered?

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Multi-Pathway Signal Blockade

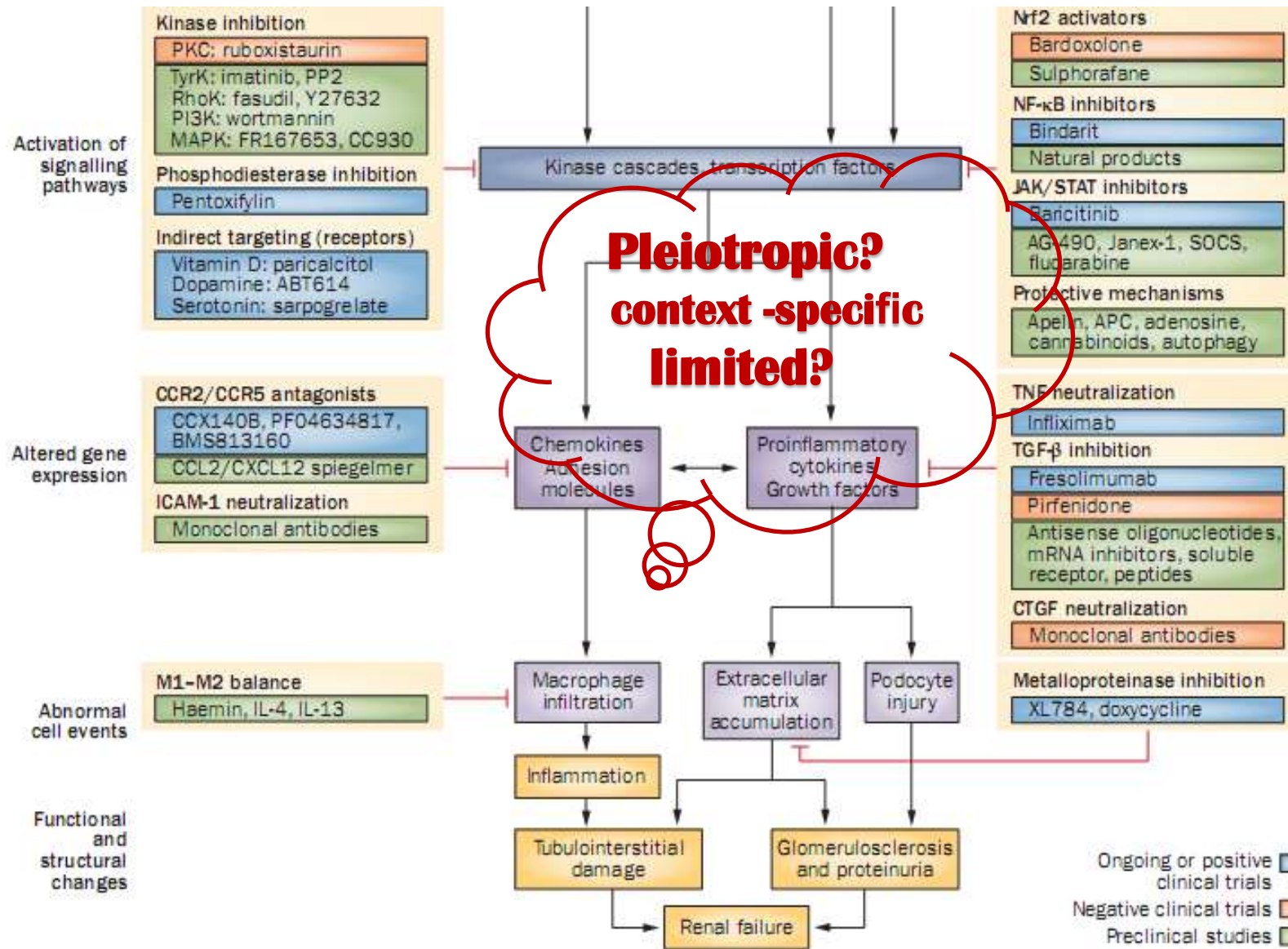
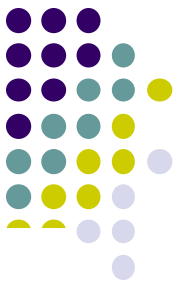
Novel Approaches to DKD



Beatriz et al., Nature Reviews 2014



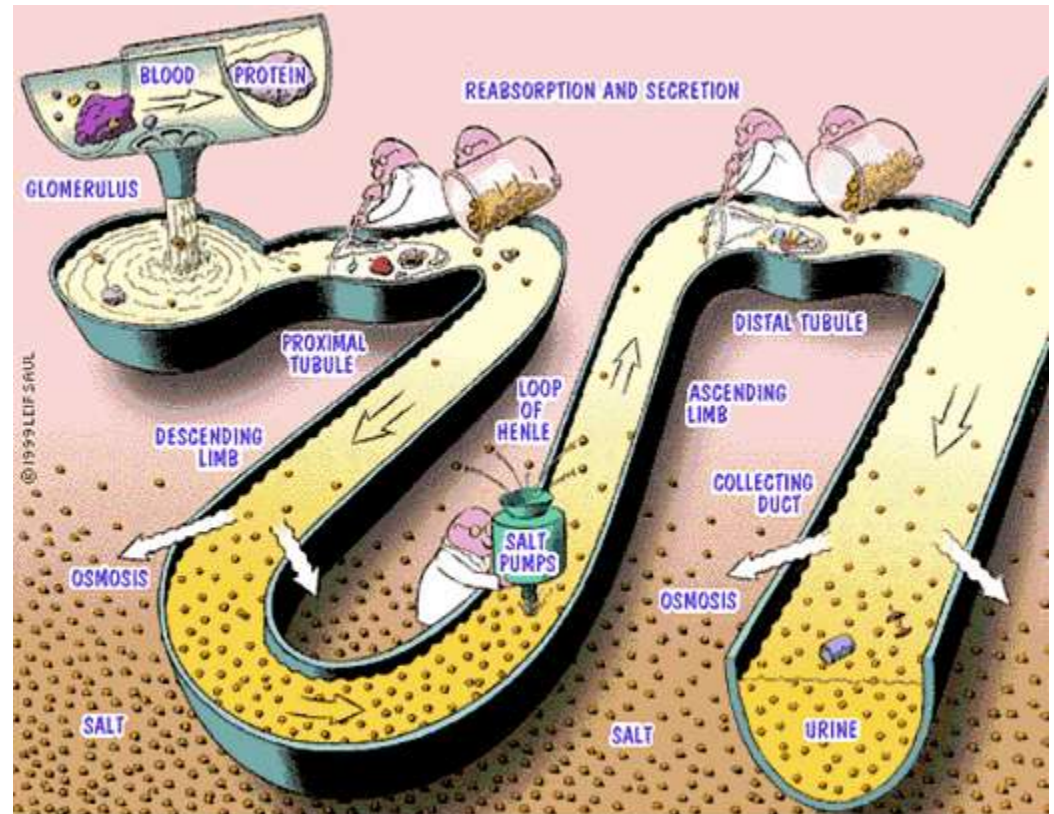
Novel Approaches to DKD



In Summary....



□ Care
for
Glomerulus
but
Mind the
Tubules !



Thank You.

